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A Monthly Review of Surgical Science and Practice

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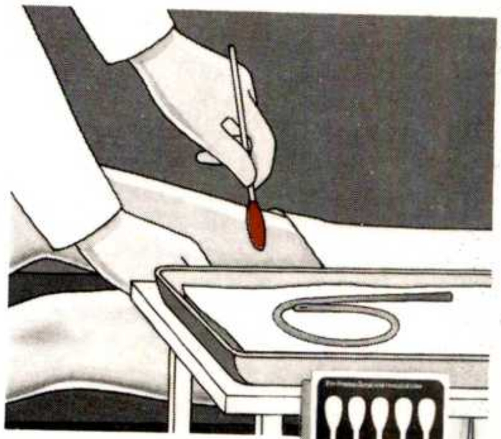

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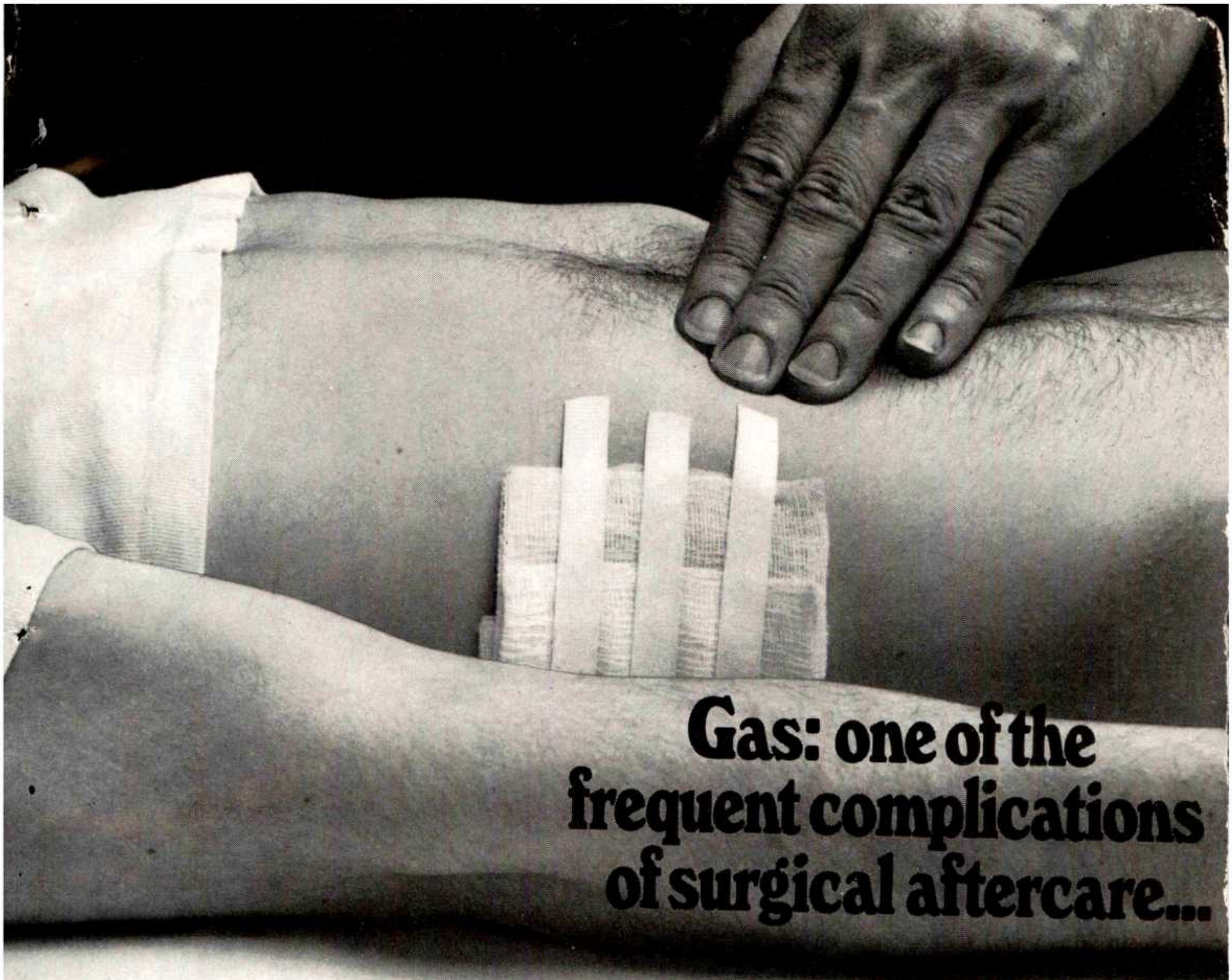
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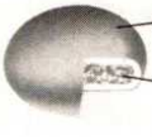

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.
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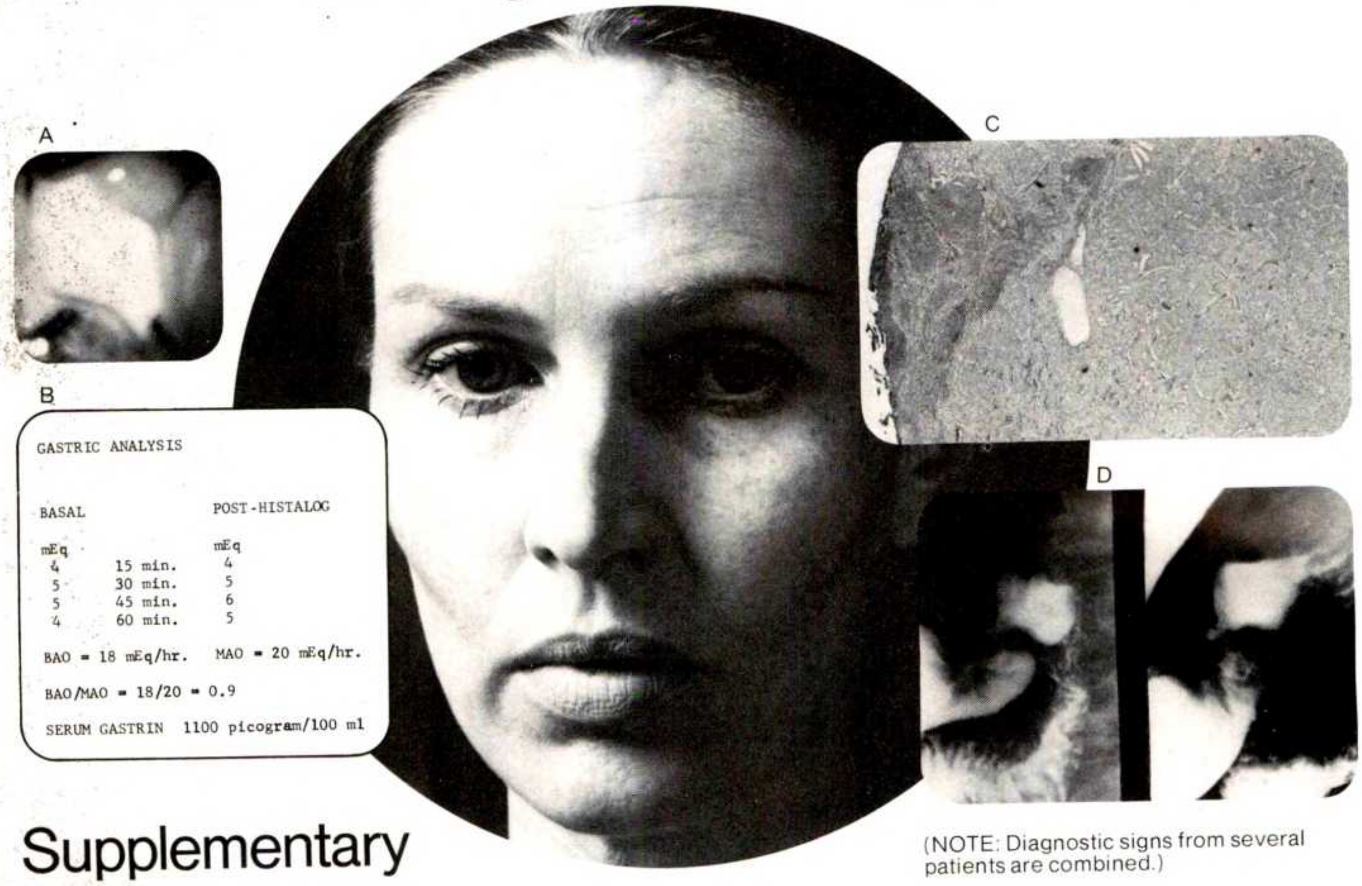

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BASAL mEq		POST-HISTALOG mEq
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4	60 min.	5

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**Diagnosis appears on next page.*

See next page for summary of Product Information.

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DIAGNOSIS: Zollinger-Ellison Syndrome is revealed in these illustrations: (A) Endoscopic view showing multiple marginal ulcers; (B) Gastric provocation secretion studies showing high basal secretion rate with marginal increase on HISTALOG provocation and elevated serum gastrin; (C) Lymph node biopsy showing pancreatic islet alpha-cell tumor spread; (D) Barium meal showing a duodenal ulcer.

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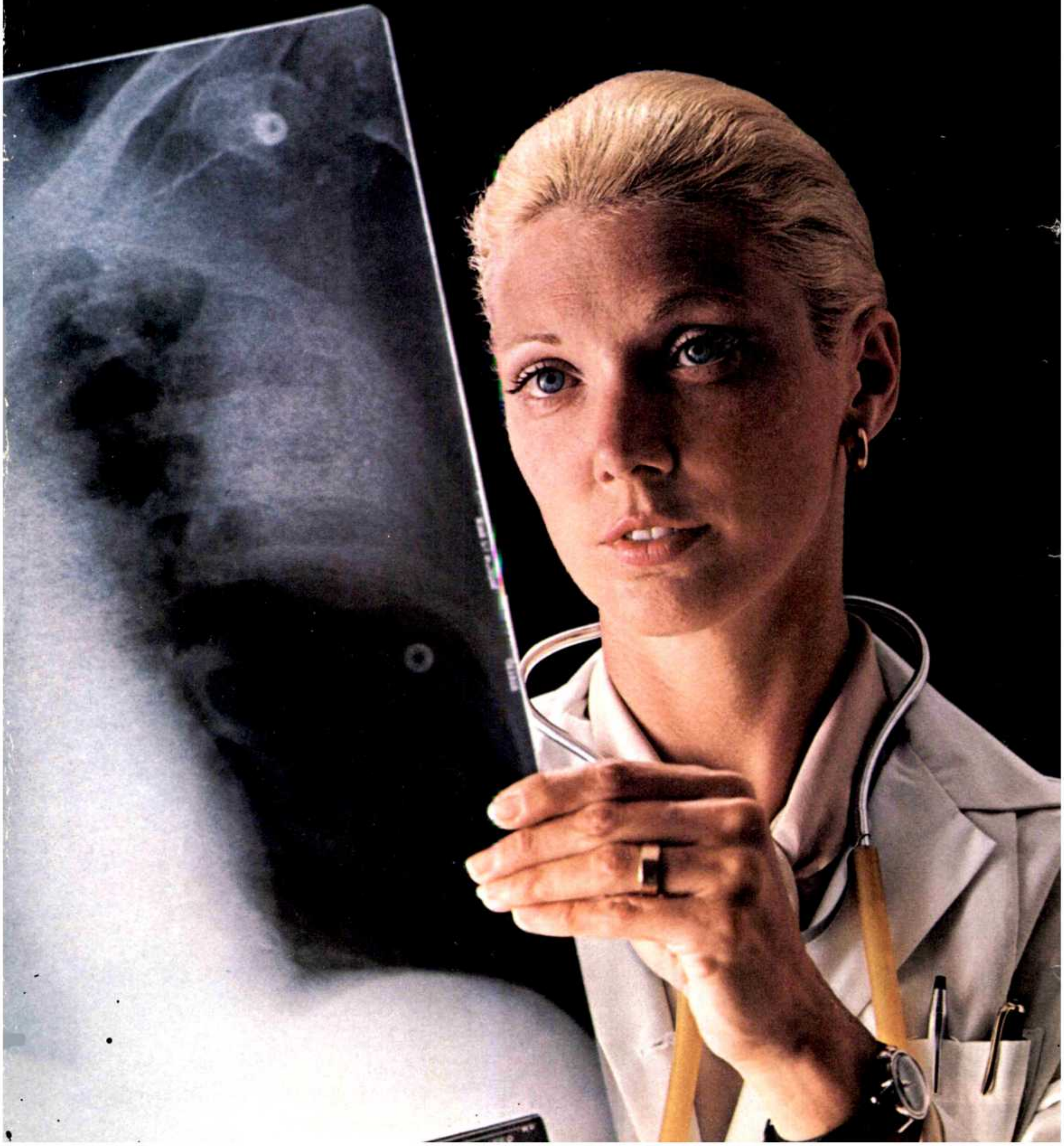
In serious respiratory tract infections*

*due to susceptible microorganisms



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- **With 93% efficacy in respiratory tract infections.**
  In clinical trials, 'Ancef' produced good or excellent responses* in 93% of 377 patients with respiratory tract infections due to susceptible organisms (See Indications section of brief summary for list of organisms).
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  Following single 1 gram IV injections in healthy adult volunteers, 'Ancef' produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.
- **With a low risk of phlebitis at the IV injection site.**
  Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. These data were derived from pre-marketing clinical studies in small populations. While further clinical experience may reveal a greater incidence of adverse effects, it should be noted that the incidence of known phlebitis has not increased with over a year's clinical experience since introduction.
- **With no reported nephrotoxicity.**
  (Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without evidence of renal or hepatic impairment.)
- **With the flexibility of IV or IM administration.**

Adverse Reactions

Adverse reactions reported in clinical trials included pain on injection, rash, G.I. symptoms, pruritus, and phlebitis. For a complete list of adverse reactions reported with 'Ancef' therapy, please see next page.

Warning: In penicillin-allergic patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity.

*(Excellent response: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good response: Initial improvement at 2-4 days with maximum improvement between 4-10 days. Results collected from identical clinical protocols.)

See next page for a brief summary of the prescribing information.

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Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

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STERILE CEFAZOLIN SODIUM

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus *(P. vulgaris, P. morgani, P. rettgeri)* are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram+ cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

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Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

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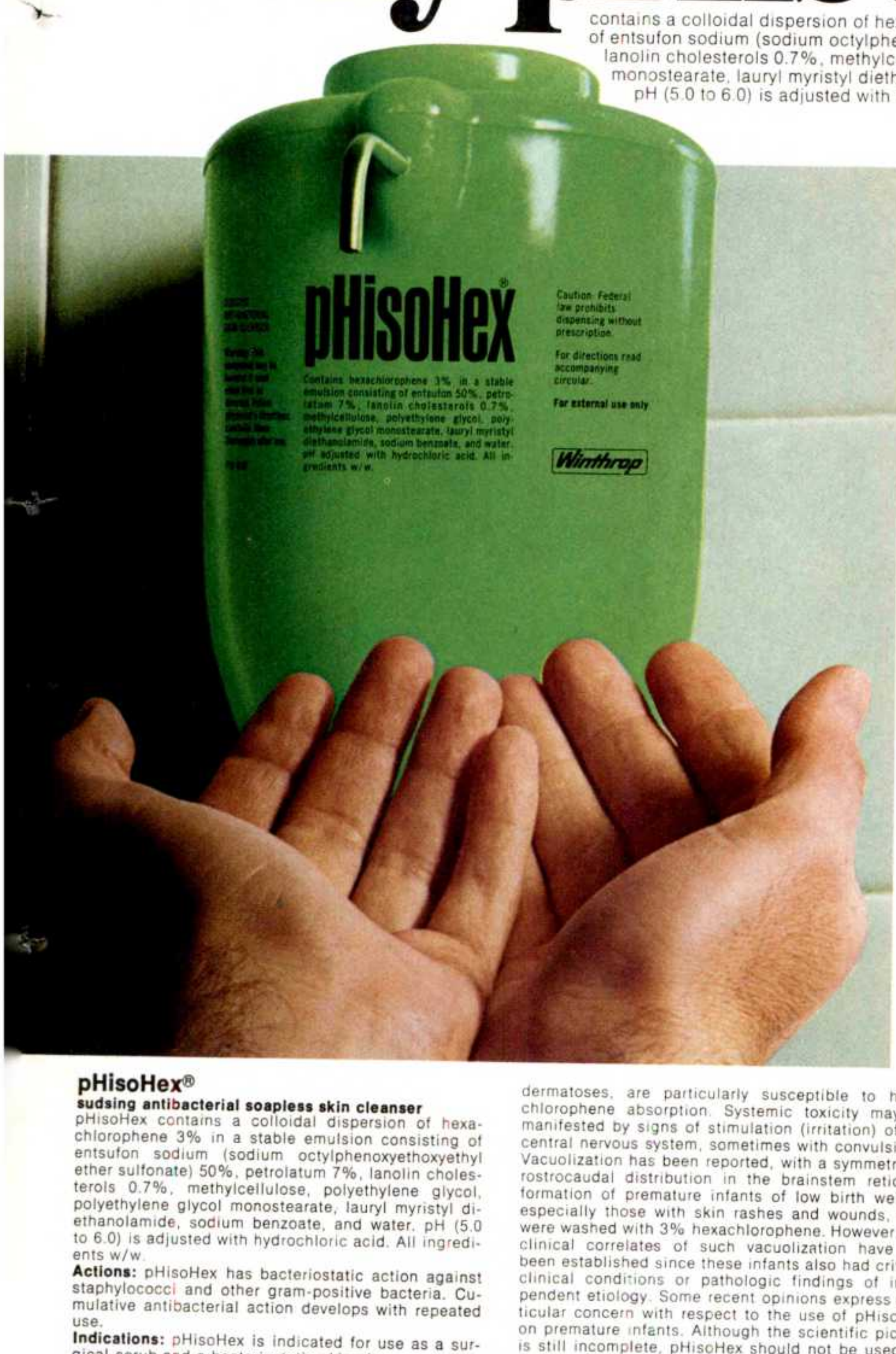
contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.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Nonalkaline, hypoallergenic pHisoHex is clearly indicated for staphylococci and other gram-positive bacteria as a bacteriostatic hand cleanser and surgical scrub. *Rinse thoroughly after use.*

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Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTEh USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

PHISOHEX SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only.* If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

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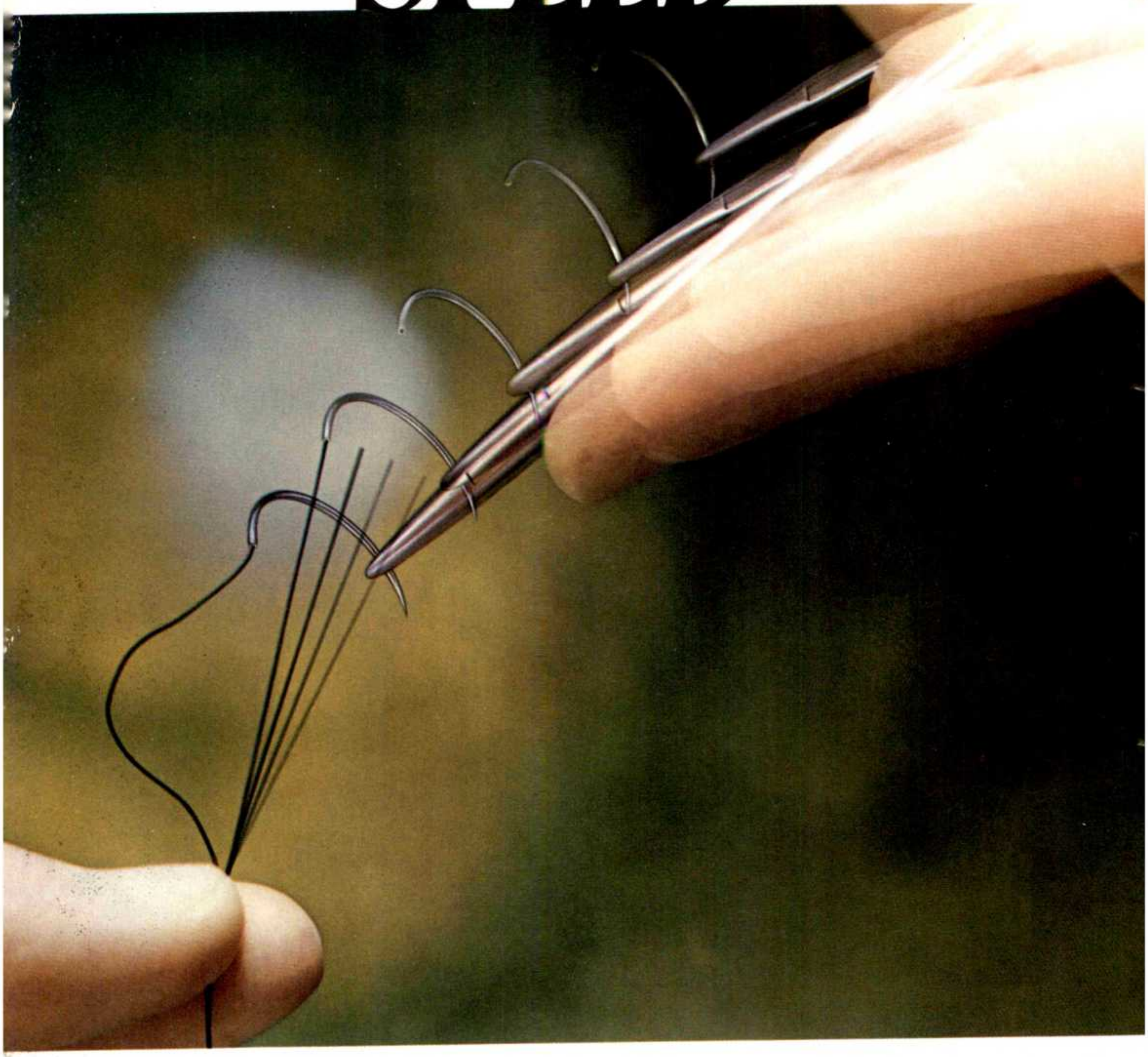

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Sequential Changes in Cerebral Blood Flow and Distribution of Flow Within the Brain During Hemorrhagic Shock

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Sequential changes in cerebral blood flow as well as in regional blood flow to the brain (brain stem, cerebellum, hypothalamus, white matter and grey matter) were measured in unanesthetized dogs subjected to gradual prolonged hemorrhage according to a protocol which stimulates the most commonly encountered type of clinical hemorrhagic shock. Microspheres labeled with five different radioactive isotopes were injected into a left atrial catheter at five different times: control, early hypotension (immediately after hemorrhage), late hypotension (just before reinfusion of the shed blood), as well as one and eight hours after reinfusion of the shed blood. Immediately after hemorrhage, the total cerebral blood flow decreased slightly, but increased when calculated as a percent of the cardiac output. In the late hypotensive, hypovolemic stage, there was decreased flow calculated both as percentages of cardiac output and absolute flow as compared with the initial response to hemorrhage. Immediately after reinfusion of the shed blood, there were further reductions of flow. Eight hours subsequently, flow rose to values slightly above control. The patterns of each region was almost identical to that of the total cerebral flow. Since each of the major regions of the brain are approximately equally affected, changes in the level of consciousness and other cerebral functions occurring with hypovolemic shock may reflect circulation of the white matter as well as that of the whole brain.

TECHNICAL DIFFICULTIES in the measurement of cerebral blood flow have made this organ one of the most difficult areas to study. The classical method for determining cerebral blood flow was developed by Kety and Schmidt[10] who used a modification of the Fick principle with nitrous oxide, an inert gas, as the indicator. Subsequent investigations[13,14] introduced isotopically labeled inert gases, such as ^{85}Kr and ^{133}Xe, to measure cerebral blood flow. By placing several collimated gamma connecters outside the skull, simultaneous tissue washout curves were constructed after arterial injection of the radioactive gas. Analysis of tissue washout curves were used to calculate regional blood flow as well as white and grey matter blood flow.

Other methods for measuring cerebral blood flow have included the measurement of the fraction uptake of ^{131}I labeled iodoantipyrine,[15] the use of electromagnetic and ultrasonic flow meters;[22] and the use of heated thermocouples to measure blood flow by a thermal indicator dilution technique.[5]

Rudolf and Heyman[18] introduced the use of radioactive labeled microspheres to study the distribution of cardiac output and regional blood flow. Several investigators have demonstrated the validity of this method for measuring blood flow.[8,9] In the present study, we have used this method to estimate the cerebral circulation of the unanesthetized dog. The sequential changes in the total blood flow, as well as regional flow to the brain during the course of graded hypotension and recovery were observed.

Materials and Methods

The experiments were performed on 14 mongrel dogs weighing 18–22 kg. A polyethylene catheter was placed in the left atrium through a small thoracotomy one week prior to the experiment. Catheters were placed in the thoracic aorta and right atrium under local anesthesia on the day of the experiment. The animal was then placed in a Pavlov stand and the experimental protocol was begun.

The catheters were attached to statham P23Dd pressure transducers and the pressures were recorded on an Offner Dynograph. The indicator dilation technique with in-

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docyanin green was used to measure cardiac output. A Gilford photodensitometer was used to measure indocyanin green concentrations in the arterial blood. The Steward-Hamilton formula was used to calculate the cardiac output from the dye curve.[12]

The protocol for inducing shock in the dogs has been reported in detail.[11] A schematic representation of the protocol is shown in Fig. 1. After control measurements blood was slowly removed over a three hour period until the mean arterial pressure reached 50 mm Hg. The pressure was maintained at this level by removing or reinfusing small amounts of shed blood. The blood was kept in sterile plastic blood transfusion bags using heparin as the anticoagulant; the blood was rewarmed prior to infusion. After it was necessary to return 20% of the shed blood to the dog to maintain its pressure at 50 mm Hg, the remainder of the blood was infused over one hour. Six dogs were sacrificed when they had survived 40 hours after transfusion; five dogs died during the hypotensive period.

At five different times during the protocol radioactive microspheres were injected through the left atrial catheter (Fig. 1). At the time of each injection, cardiac output as well as intravascular pressures were recorded.

The microspheres (3M Company) used were labeled with five different isotopes: ^{141}Ce, ^{76}Sc, ^{85}Sr, ^{51}Cr and ^{125}I. The microspheres were 15 ± 5μ in diameter; specific activities were about 10 mCi/g, except for ^{51}Cr which was 52 mCi/g. Approximately 0.025–0.05 mCi of each isotope was injected for each measurement.

After death or sacrifice of the animals autopsies were performed and the brain was removed from the skull and weighed. By gross dissection samples were taken of the following areas: brain stem, cerebellum, hypothalamus, white matter and grey matter. Each sample was weighed, placed in the lower third of a six-inch test tube and assayed on a Picker well-type scintillation spectrometer with dual channels. The counting was done at five different energy levels, previously determined for optimal separation of various isotopes. Each radio assay was corrected for the radio-activity of the other isotopes using appropriate standards and a formula similar to the one described by Rudolf and Heyman.[18]

The CPM/Gram for the whole brain and for each individual area were averaged and divided by the injected dose for each isotope. The results represented the percent of the cardiac output per gram of tissue. The percent cardiac output to the brain was obtained by multiplying the above value by the total organ weight. The absolute flow was obtained by multiplying percent cardiac output by the cardiac output as measured by dye dilution.

Results

The values for the sysetmic cardiac output as well as the cerebral blood flow, expressed as a percent of cardiac ouput and as the absolute blood flow to the brain, at each of the time periods studies are shown in Fig. 2. There was a marked rise in the cerebral blood flow as a percent of cardiac output in the early hypotensive period, but a slight fall in the late hypotension period; there was a large decrease one hour after transfusion to near control values. The eight hour post-transfusion value was slightly above control.

Figure 3 summarizes the data for the regional distribution of cardiac output to the different areas of the brain studied. The general pattern of each region is almost identical to that of the total brain. Each area differs only in absolute value of percent cardiac output with the grey matter

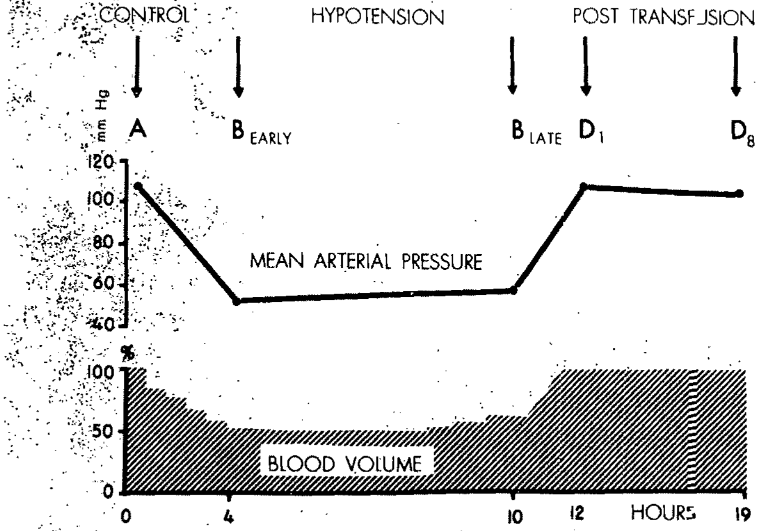

FIG. 1. The protocol illustrating mean arterial pressure and blood volume changes during the experiment. The labeled microspheres were injected at the time indicated by the arrows: control period (A), early hypotension (B early), late hypotension (B late), one hour post-transfusion (D_1), and eight hours post transfusion (D8).

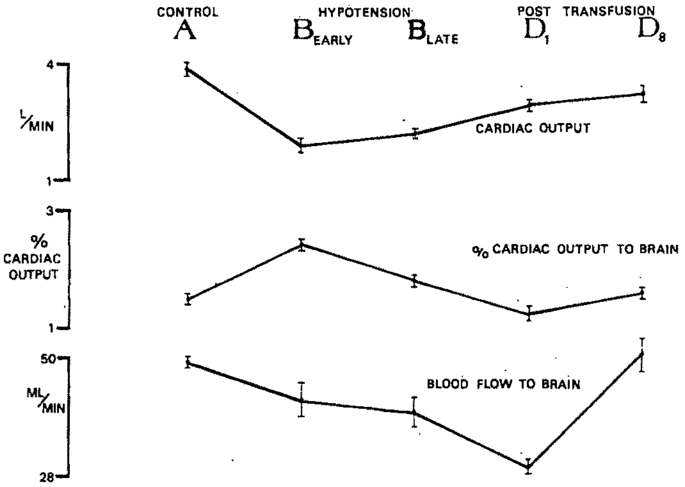

FIG. 2. The mean systemic cardiac output (± one standard error of the mean); the percent of cardiac output to the brain (± 1 standard error of the mean); and the total blood flow to the brain (± 1 standard error of the mean); at each stage of the experiment.

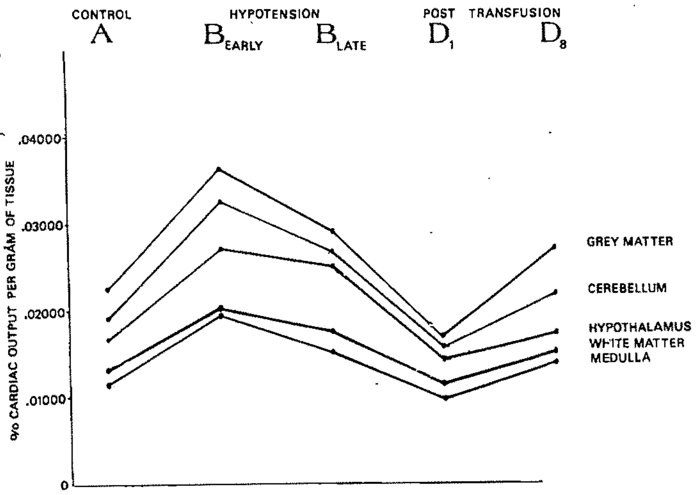

FIG. 3. The percent cardiac output (per gram of tissue) to various parts of the brain at each stage of the experiment.

having the highest percentage and the medulla having the least of those areas examined. The ratio of grey matter to white matter in the control period was 1.84:1.

The arterial blood gas data is presented in Figure 4. There was little change in the arterial oxygenation. The arterial pCO_2 decreased during the hypotensive period and then returned towards normal after transfusion.

Discussion

The response of the cerebral circulation to hemorrhage hypotension has been reported by several investigators [3,20] as well as ourselves.[19] There was a rise in the percent cardiac output to the brain and only a modest reduction in the absolute blood flow. This pattern is thought to occur mainly as a passive phenomenon in which a larger proportion of the total blood flow goes to the brain because of the increased resistance to flow in those organs sensitive to alpha adrenergic activity; that is, the gastrointestinal tract, kidney, spleen and skin.[6] The circulation to the brain has been shown to respond poorly to catecholamines.[4]

The fall in arterial pCO_2 that resulted from hyperventilation in the animals would be expected to produce cerebral vasoconstriction with decreased cerebral blood flow.[16] It is likely that the systemic acidosis, secondary to poor tissue perfusion, and the concomitant fall in extracellular cerebral pH was a significant factor in increasing cerebral blood flow.[1] Arterial oxygen tension did not change appreciably and probably was not an important factor in this study.

The decrease in the percent of cardiac output to the brain between the early and late hypotensive stages, although still above control values may have been due to a decrease in the neurohumoral responses in this period.[2,21] The effect of an even lower arterial pCO_2, with a rise in arterial pH, represents respiratory compensation for systemic as well as cerebral acidosis; this may have contributed to the fall in cerebral blood flow.

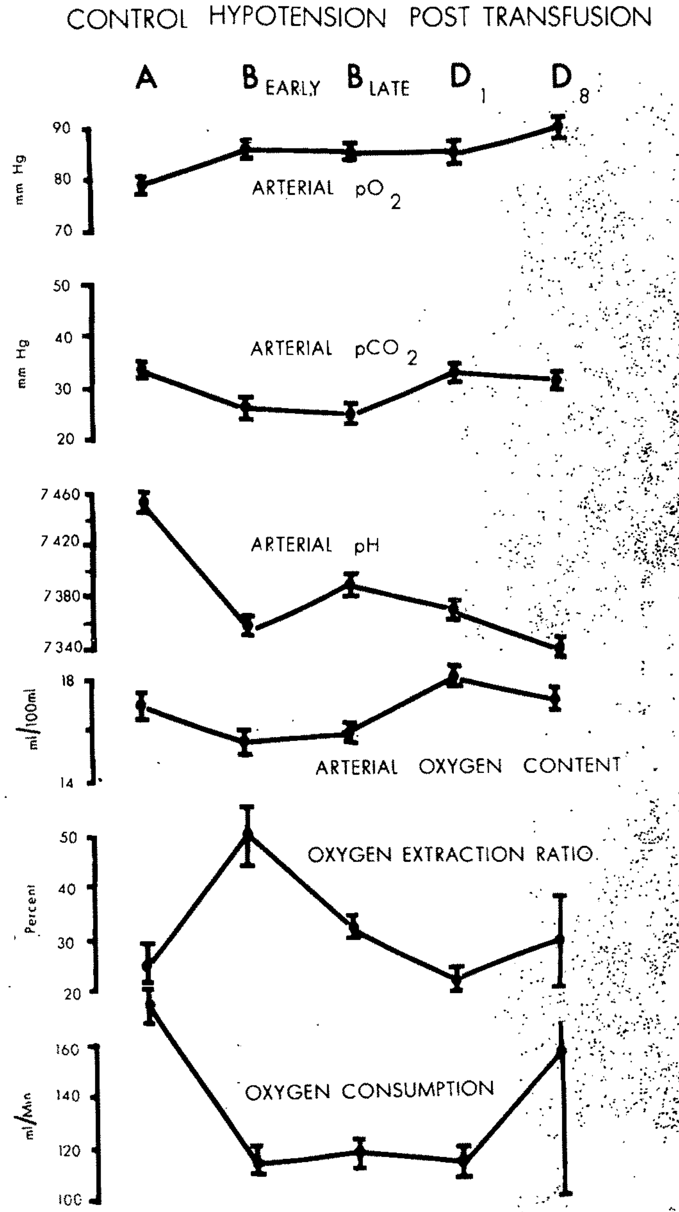

FIG. 4. Blood gas values. The mean ± 1 standard error of the mean for arterial pO_2, pCO_2, pH, oxygen content.

After the return of blood volume to the animals, the percent of cardiac output to the brain decreased to near control values. This reflects the redistribution of blood to areas of the body where resistance decreased in response to transfusion. Since arterial pCO_2 values increased only slightly after transfusion, this could not be the major regulatory mechanism operative at this stage.

The basic patterns in the redistribution of cardiac output and regional blood flow in each anatomic area of the brain studied were approximately the same from period to period. Each area differed only in the absolute quantity of blood flow and not the percentage of cardiac output. This would imply that the mechanisms regulating flow to the brain in the dog are similar in each area. The ratio of grey matter flow to white matter flow remained relatively constant throughout the study. The ratio of slightly less than 2:1 is less than that reported both by Roth *et al.*[17] using microspheres and by those using the ^{85}Kr clearance technique;[7] however, this disparity may be due to differences in the techniques of anatomic dissection.

The data are consistent with the view that circulatory changes to the major segments of the brain are relatively equally affected and that major redistributions of flow favoring the brain stem or other primitive areas do not occur under the conditions of these experiments. This suggests that the degree of cerebral impairment associated with the hypovolemic low cardiac output state may reflect its circulatory status and that manifestations of cortical function may be a useful index of the circulation of the whole brain.

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Hepaticogastrostomy:

Ulcerogenic Preparation or Therapeutic Alternative

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Recent laboratory and clinical studies have implicated bile salts in the pathogenesis of gastric ulceration. Common hepatic duct to stomach anastomosis results in total diversion of bile to the stomach and has been utilized at the Lahey Clinic occasionally for bypass of the obstructed common bile duct in difficult technical situations where conventional procedures were deemed prohibitively difficult. Of seven patients undergoing hepaticogastrostomy, two had upper gastrointestinal bleeding in followup. One of these patients had documented esophageal varices and stopped bleeding after splenorenal shunt. The other had massive sepsis which predisposed him to gastric ulceration. From this small series it is clear that the entire biliary output of the liver can be shunted into the stomach without greatly increased risk of clinically significant gastric ulceration. Hepaticogastrostomy provided relief from jaundice in all but one of the seven patients in the series and remains an occasionally useful procedure. These data indicate that diversion of the entire flow of bile from the liver into the stomach does not cause gastric ulcers.

HEPATICOGASTROSTOMY has occasionally been utilized in the Lahey Clinic operative experience with bypass of biliary obstruction. The patients treated with this procedure have, for various anatomic reasons, been unsuitable for anastomosis of the proximal hepatic duct to either the distal duct, jejunum, or duodenum, all of which we have considered preferable.[3,10]

An analysis of the results will be helpful to a surgeon contemplating performing this procedure. This is especially true because of recent clinical and laboratory studies which suggest that bile is extremely damaging to the gastric mucosa. Bile salts have been shown to disrupt the gastric mucosal barrier to hydrogen ion,[4] to release gastrin from the antrum and thereby increase gastric acidity,[9] and, indeed, to produce gastric ulceration in shocked experimental animals.[8] Clinical studies showing increased pyloric reflux in patients with gastric ulcers further implicate bile in the cause of gastric ulceration.[5-7]

It might be predicted from these studies that hepaticogastrostomy would lead to almost certain gastric ulceration and, thereby, be entirely unacceptable as a therapeutic alternative for the treatment of biliary obstruction.

Methods

A search of the records of the Lahey Clinic and its associated hospitals yielded a total of seven patients who had had hepaticogastrostomy. No specific numerical code for hepaticogastrostomy had been used in record keeping; therefore, the chart search was difficult, and it is probable that more patients with hepaticogastrostomy exist than were found in this study. Variations in the procedure were accepted only if it could be assured that the biliary tract was drained exclusively and permanently into the stomach. Procedures for distal obstruction when the distal tracts were left intact and, therefore, might conceivably regain function were excluded.

The efficacy of the procedures in relieving biliary obstruction was judged satisfactory if serum bilirubin values fell dramatically after operation either to normal values or values consistent with underlying liver disease. The procedures were rated unsatisfactory if bilirubin values did not fall.

The occurrence of peptic ulceration after operation was determined by the usual clinical criteria. A retrospective survey of patients' records was conducted. The signs and symptoms relating to hemorrhage, perforation, and obstruction were sought both during the postoperative hospital stay and in followup clinic visits. Upper gastrointestinal tract

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barium studies were performed on two of the patients during the postoperative period.

Results

Seven patients, four men and three women, fit the criteria for inclusion in this report. Six patients were operated on at the Lahey Clinic; three patients had benign obstruction and three had malignant obstruction. These patients ranged in age from 48 to 76 years. One patient had the procedure performed elsewhere for a congenital anomaly at age 3 months, and revision was carried out at the Lahey Clinic. The period of followup for the patients who survived the postoperative period ranged from four months to 21 years with no patients lost to followup. (Table 1).

Case Reports

Case 1. A 76-year-old man had had cholecystectomy at another hospital (November 1967) for a perforated, acutely inflamed gallbladder. After operation the patient had intermittent attacks of jaundice with chills and fever. The serum bilirubin level was 1.3 mg/100 ml on admission to the Lahey Clinic. At exploratory laparotomy, massive adhesions were encountered. The proximal common hepatic duct was identified with difficulty, and the nature of the distal obstruction was not determined. Neither the jejunum nor the duodenum could be brought up for anastomosis because of massive adhesions, obesity, and short fat mesentery. The stomach was in close apposition to the proximal hepatic duct and hepaticodochogastrostomy was performed. The serum bilirubin level fell to 0.4 mg/100 ml and the patient's postoperative and subsequent course has been benign until the present time. A postoperative upper gastrointestinal tract barium series (March 1970) showed the stomach free of ulcers and the hepaticogastrostomy open.

Case 2. A 48-year-old man had had painless jaundice in December 1960 and had cholecystojejunostomy performed at another hospital for "unresectable carcinoma of the pancreatic head." The patient was well for one year and nine months but then jaundice returned. At the Lahey Clinic, serum bilirubin level was 13 mg/100 ml and serum albumin 2.9 gm/100 ml. On March 21, 1963 a palliative procedure was performed consisting of hepaticodochogastrostomy, pancreaticogastrostomy, and gastrojejunostomy for a lesion of the pancreas. Postoperatively, the patient had a draining biliary fistula for 18 days with 25–100 cc of fluid a day. This closed spontaneously. At the time of discharge from the hospital, the serum bilirubin value was 3.4 mg/100 ml. The patient died from intestinal obstruction on July 29, 1963.

TABLE 1. *Hepaticogastrostomy Patients*

Case, Age, and Sex	Diagnosis	Period Followup	Cause of Death
1 76 M	Stricture	4 yrs	Alive
2 48 M	Carcinoma pancreas	4 mos	Carcinoma
3 52 F	Stricture	6 yrs	Hepatic failure
4 52 M	Stricture	2 yrs, 3 mos	Alive
5 67 F	Carcinoma bile duct	10 days	Sepsis
6 21 F	Congenital atresia	21 yrs	Alive
7 59 M	? Carcinoma pancreas	21 days	Gastric hemorrhage, sepsis

Case 3. A 52-year-old woman had had cholecystectomy (February 1962) with resulting biliary stricture. Roux-en-Y jejunal anastomosis to the common hepatic duct was performed (April 1962) and revised for recurrent jaundice (April 1964). When jaundice recurred in March 1965, the patient came to the Lahey Clinic. On admission here, jaundice with ascites was evident. Serum bilirubin value was 9.3 mg/100 ml and serum albumin value was 2.9 gm/100 ml. At exploratory laparotomy (July 22, 1965) the stricture was repaired with difficulty using a gastric anastomosis to the right and left hepatic ducts separately, and sludge was removed from the biliary tree.

The liver was cirrhotic, and ascites, splenomegaly, and portal hypertension were evident. The postoperative course was complicated by a biliary fistula, which closed on the 24th day after operation, and by persistent sepsis, intestinal obstruction, and occasional upper gastrointestinal tract bleeding. On November 13, 1965 the serum bilirubin value was 2.3 mg/100 ml and she was discharged to her home. The patient was well initially, but transfusions were required for hematemesis and melena in August 1968 and March 1969. Upper gastrointestinal tract barium studies showed esophageal varices; the stomach and duodenum were free of ulcers on these occasions (Figs. 1 and 2). Splenorenal shunt was performed April 25, 1969. Intestinal hemorrhage did not recur. The patient died from hepatic failure in August 1971.

Case 4. A 52-year-old man underwent cholecystectomy March 29, 1971 at which time the common bile duct was divided. Choledochoduodenostomy and gastrojejunostomy were performed. Later, because of obstruction at the gastrojejunostomy, a more distal gastroenterostomy and enteroenterostomy were carried out. When jaundice recurred (October 1970), the patient came to the Lahey Clinic. Jaundice was present with a serum bilirubin value of 5.9 mg/100 ml. During operation, performed on March 29, 1971, the duodenal anastomosis was disconnected, and the duodenum was closed. Hepaticogastrostomy was performed. The postoperative course was favorable with lessening of jaundice, and serum bilirubin value was 3.6 mg/ 100 ml at the time of discharge. The patient has done well and has been free of jaundice to the present time.

Case 5. A 67-year-old woman had had cholecystectomy May 25, 1959. The common duct was explored because of small stones, and the duct was judged normal. The patient was well until November 1959 when jaundice appeared; operation (April 21, 1960) revealed a 3 mm common duct stricture. A T tube was placed, and the patient was transferred to the Lahey Clinic. During operation (May 11, 1960) biopsy specimen of the strictured region was taken and adenocarcinoma simplex was found. Hepaticogastrostomy was created for palliation; the entire porta hepatis was involved with tumor. The patient had a septic course with a biliary fistula and a rising serum bilirubin level and died on the 10th postoperative day.

Case 6. A 21-year-old woman had had bypass of distal common bile duct atresia at the age of 3 months by anastomosis of a distal choledochal cyst and the gallbladder to the stomach. The patient had no signs of intestinal hemorrhage or cholangitis. At the age of 21 the patient became jaundiced and was referred to the Lahey Clinic. An upper gastrointestinal tract barium series showed the stomach and duodenum to be free of ulcers. At operation (November 4, 1968) the cystic duct was obstructed with narrowing of the choledochocystogastrostomy. Cholecystectomy and choledochocystojejunostomy were performed. The postoperative course was uneventful.

Case 7. A 59-year-old man had had exploratory laparotomy at another hospital for painless jaundice. A mass was found in the head of the pancreas, and a T tube was placed in the common bile duct. The postoperative course was complicated by sepsis and shock, and he was transferred to the Lahey Clinic. At operation, subhepatic and subphrenic abscesses were present as well as biliary and duodenal fistulas. The abscesses were drained, the duodenal fistula was closed, and choledochogastrostomy and gastrojejunostomy were performed. After operation, the patient had a myocardial infarction with pulmonary edema, continuing sepsis and shock, and hemorrhage. On the 10th postoperative day, blood appeared in the nasogastric tube and persisted intermittently until the patient's death 13 days later. During this period, 19 units of blood were given. No diagnostic procedures were undertaken to determine the exact origin of the upper gastrointestinal tract hemorrhage because of the patient's multiple problems and moribund condition. Autopsy was refused.

Comment

Relief of Jaundice

Relief of jaundice was satisfactory in five of the seven patients, unsatisfactory in one of the patients, and unknown but probably satisfactory in the seventh patient. The preoperative and postoperative serum bilirubin values, when available, are shown in Table 2.

Gastric Ulceration

Two of the patients had clinically significant upper gastrointestinal tract hemorrhage after hepaticogastrostomy. One patient (Case 7) had massive upper gastrointestinal tract hemorrhage coincident with septic shock which led to his death. This patient also had massive sepsis and shock, which were additional predispositions to gastric hemorrhage. The other patient (Case 3) had upper gastrointestinal tract hemorrhage requiring transfusion in the immediate postoperative period and twice thereafter. Barium swallow examination showed esophageal varices with normal stomach and duodenum. After splenorenal shunt, the patient was free of clinically significant hemorrhage for the ensuing two years and four months until her death from hepatic failure.

The remaining four patients who had functioning hepaticogastrostomies (Cases 1, 2, 4, and 6) were free of the signs and symptoms of gastric ulceration for significant periods of followup (4 yrs, 4 mos, 2 yrs 3 mos, and 21 yrs respectively).

Postoperative upper gastrointestinal tract barium studies confirmed the absence of gastric ulceration in three patients (Cases 1, 3, and 6).

Discussion

As a bypass procedure for the relief of biliary obstruction and jaundice, hepaticogastrostomy, while rarely necessary, clearly has some merit. Five of the seven patients (71%) had prolonged relief of jaundice and in only one patient (Case 5) was the procedure ineffective in relieving jaundice. This compares satisfactorily with reports of other bypass procedures from the Lahey Clinic. Hepaticojejunostomy has provided prolonged relief from benign stricture in 75%[2] and 43%[3] of patients, end-to-end biliary anastomosis in 75%[2] and 51%[3], and hepaticoduodenostomy in 50%[3]. Precise comparisons of the relative merits of the operations in these patients is not possible because the patients were not matched for severity of stricture in any of the series.

The two postoperative deaths in this series (29%) can be explained partially by the fact that hepaticogastrostomy has been reserved for the most difficult technical situations—usually obese patients who have had multiple previous bypass operations. One patient (Case 5) had advanced cancer and died with an anastomotic leak. The other patient (Case 7) had an extraordinarily difficult preoperative septic condition, and operation was ineffectual in reversing the septic course. The postoperative death rate for benign stricture repair has been 5% or less for the commonly performed procedures of hepaticojejunostomy or duodenostomy as well as end-to-end repair in the Lahey Clinic experience.[3]

Regarding the propensity of hepaticogastrostomy to cause gastric ulceration, it is clear that the procedure creates only a mild predisposition to clinically significant gastric ulceration. None of the patients had gastric perforation, obstruction, or pain typical of gastric ulceration. Of the two patients with upper gastrointestinal tract hemorrhage, one (Case 3) obtained relief by splenorenal shunt thereby strongly suggesting that the patient's radiographically proved esophageal varices rather than gastric ulceration were the cause of the bleeding. The other patient (Case 7) had massive hemorrhage from presumed gastric stress ulceration. This patient was in septic shock with biliary and duodenal fistulas and intra-abdominal abscesses, however, which provided an additional predisposition to gastric ulceration. The remaining four patients (Cases 1, 2, 4, and 6) who had bypass of the entire biliary output into the stomach for long periods of followup were without clinical evidence of gastric ulceration.

It is questionable why bile salts, which have experimentally been shown to be damaging to the gastric mucosa, are

TABLE 2. *Relief of Obstructive Jaundice by Hepaticogastrostomy*

Case	Bilirubin Level, mg/100 ml Admission	Postoperative	Underlying Liver Disease	Rating
1	1.3	0.4	None	Satisfactory
2	13.0	3.4	Massive liver metastases	Satisfactory
3	9.3	2.4	Cirrhosis	Satisfactory
4	5.9	3.6*	None	Satisfactory
5	2.5	8.2	None	Unsatisfactory
6	Jaundiced	Free of jaundice	None	Satisfactory
7	1.8	No jaundice	None	? Satisfactory

* Serum drawn on postoperative day 16. Patient was and presently remains free of jaundice.

not more damaging in this clinical situation. Bile salts have been implicated in the cause of gastric ulceration by laboratory investigations showing that they damage the gastric mucosa by breaking the gastric mucosal barrier to acid,[4] stimulate acid secretions,[9] and even cause physical changes in the gastric mucosa.[1] Using several different methods, clinical studies have identified increased pyloric reflux in patients with gastric ulcer.[5-7]

The ulcerogenicity of bile salts in the clinical setting is brought into question by the general absence of ulcer symptoms in these patients after hepaticogastrostomy. Whether this report is evidence that bile salts are not ulcerogenic in the clinical setting or whether it is an example of an unusual circumstance in which bile salts are not ulcerogenic is not certain. Hepaticogastrostomy is a satisfactory surgical procedure without extraordinary ulcerogenic potential, and one that is occasionally useful to the clinician. In this small series, it does not appear that the diversion of the entire hepatic flow of bile into the stomach is ulcerogenic.

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The Surgeon, the Surgery, the Patient, and the Disease:

Factors Complicating Colonic Surgery

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A review of 231 cases of colonic operations performed during the year 1971 by, or under the supervision of, 32 attending surgeons in an 850 bed private community medical center was undertaken. The overall mortality rate was 5.6% while a 35.5% overall complication rate was also noted. Factors significantly associated with increased overall complication rate were: emergency operations, preoperative anemia (hemoglobin less than 10 gm%), preoperative hypoalbuminemia (serum albumin less than 3 gm%), preoperative obstruction, malignant lesions of the colon and ulcerative colitis, prolonged operation, operations requiring a large quantity of packed cell transfusion, coexisting hepatic disease and operations performed by surgical attending staff under 50 years of age in this institution. Each of these factors is discussed individually. Several factors that were expected to be associated with increased complication rate failed to show significant statistical correlation in this series. These are: age of the patient, coexisting diseases other than hepatic disease, absence of prophylactic parenteral antibiotics, preoperative perforations and operations involving resection of the colon. Hypotheses are offered to explain a number of unexpected poor correlations.

THE MORTALITY RATE of colonic surgery has decreased significantly in the last 70 years. At the turn of this century, operations for colonic carcinoma had a mortality rate of 30–50%. With the advent of better surgical techniques, safer anesthesia, the discovery of antibiotics, provisions for blood transfusions, better understanding of fluid and electrolyte balance, and overall improvement in preoperative preparation and postoperative management, we have witnessed a steady reduction in the fatality rate of the same procedures to 3–5% in some limited series. In the National Halothane Study, analysis of 15,100 large bowel operations in 34 institutions showed an overall mortality rate of 5.7%,[21] a figure more representative of surgical practice in the United States as a whole.

Non-fatal complications, however, are still common findings following colonic surgery. They inevitably prolong a patient's suffering and convalescence. His extended stay in the hospital and corresponding hours lost from work further increase the financial burden of his illness. It is important to realize that many of these disturbing non-fatal complications may be preventable if we recognize the relevant factors.

This study was undertaken to determine the mortality rate and early postoperative complication rate of colonic operations performed in an 850 bed voluntary teaching medical center in which all patients are treated as private patients operated upon by, or under the supervision of, graduate surgeons. Attempts were made to identify various factors that show a statistically significant correlation with increased overall complication rate. Comparisons with other series were also made to offer perspective to our findings.

Materials and Methods

The hospital records of all patients who underwent colonic or rectal surgery, other than minor anorectal surgery at Saint Barnabas Medical Center, from January 1, 1971 through December 31, 1971 were reviewed in detail. The following parameters were studied.

1. Postoperative diagnosis
2. Procedure performed.
3. Postoperative complications, including death.
4. Presence of coexisting disease other than that for which the patient was operated.
5. Time from day of surgery to discharge.
6. Designation as elective or emergency procedure.
7. Presence or absence of preoperative perforation.

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8. Hemoglobin level preoperatively prior to transfusion.
9. Presence or absence of colonic obstruction preoperatively.
10. Preoperative serum albumin level.
11. Number of units of packed cells (250 ml) or whole blood (500 ml) transfused at surgery.
12. Duration of operative procedure.

Occurrence of postoperative complications was determined by examination of progress notes, temperature record, nurses' notes, and laboratory and radiology reports. Paralytic ileus was defined as non-function of the gastrointestinal tract for more than seven days. Radiologic diagnosis of atelectasis and pneumonia was accepted. Intestinal obstruction was diagnosed on clinical and radiologic grounds. Pulmonary embolism was diagnosed by a combination of clinical, electrocardiographic, laboratory, and radiologic findings. Septicemia was diagnosed by positive blood culture in compatible clinical setting. Urinary tract infection was defined as urine colony count greater than 10^6/ml associated with clinical infection. Urinary retention was defined as need for prolonged foley catheter drainage. Renal failure was defined as progressive rise in BUN and serum creatinine. Respiratory failure was defined as progressive abnormality in arterial gases with requirement of respiratory support. The remainder of the complications were diagnosed by generally accepted criteria which need not be further detailed here.

In the evaluation of all factors which appeared to be related to the rate of early postoperative complications, statistical analysis using the chi-square test or the t test for small samples was carried out.

TABLE 1. *Complications of Colon and Rectal Surgery in 231 Cases*

Complication	Number of Cases
Paralytic ileus	5
Atelectasis	4
Hemorrhage	1
Pneumonia	6
Intestinal obstruction	1
Pulmonary embolism	6
Septicemia	8
Thrombophlebitis	4
Cerebrovascular Accident	1
Wound dehiscence	4
Wound infection	32
Entero-cutaneous fistula	8
Anastomotic leak	3
Colostomy complication	4
Urinary tract infection	14
Urinary retention	6
Renal failure	2
Intra-abdominal abscess	4
Acute pulmonary edema	2
Bleeding stress ulcer	3
Hepatic failure	1
Acute acalculous cholecystitis	1
Decubitus ulcer	1
Acute gastric dilatation	1
Acute toxic psychosis	1
Diarrhea	1
Strangulated right inguinal hernia	1
Cardiac arrest at surgery	1
Atrial fibrillation and left bundle branch block	1
Peritonitis	1
Respiratory failure	2
Slough of skin edges of incision	1
Rectovaginal fistula	1
Gouty arthritis	3
Acute cholecystitis	1
Obstructive jaundice	1
Left pleural effusion	2
Left empyema	1
Perineal abscess	1
Drug dependence	1
Arrhythmia	1
Total	143

82 operations were followed by complications. Overall complication rate 35.5%.

Results

A total of 231 cases were analyzed, representing all cases of colonic and rectal surgery, except minor anorectal surgery, at Saint Barnabas Medical Center for the year 1971. Twenty-nine different types of procedure were performed. The operations were performed by 32 members of the attending staff, ranging in age from 32 to 71 years. Twenty-nine different diseases were treated by colonic and rectal surgery; 143 complications occured in 82 cases (Table 1). Thus, the overall percentage of cases followed by complications was 35.5%. The actual number of patients who developed one or more complications was 77, since some patients were operated upon more than once during this time period. The number of deaths in this series was 13. Mortality rate was 5.6% overall.

Forty-five cases were performed as emergencies. The complication rate of 53% in these cases was significantly greater ($p < 0.01$) than the complication rate of 31% for elective cases. Eight deaths occurred following emergency operations. Twenty-one patients had preoperative hemoglobin less than 10 g before transfusion. The complication rate in this group was 57%, compared to the complication rate of 33% with patients with higher preoperative hemoglobin. The difference was statistically significant ($p < 0.05$). Twenty-three patients had a serum albumin of less than 3 g. The complication rate in this group was 57%. This was significantly greater than the complication rate of 34% for patients with a higher preoperative level of serum albumin ($p < 0.046$). Thirty-five patients were obstructed preoperatively. Complications occurred in 57% of these cases, which was a significantly greater rate of complications than the 32% for patients who were not obstructed preoperatively ($p < 0.005$). Patients who developed complications were found to have received significantly larger volumes of packed cells or blood at surgery than patients who did not develop complications (Table 2). Patients who developed complications were found to have had significantly longer operative procedures than patients who

TABLE 2. *Complications and Blood Transfusions*

	Total Cases	Mean Number of Units of Packed Cells Given at Surgery	
Complicated cases	82	0.52 ± 0.97	t = 2.47 n = 229
Uncomplicated cases	149	0.24 ± 0.73	0.01 less than p less than 0.02

TABLE 4. *Complications and Chronic Ulcerative Colitis*

	Total Cases	Complication Rate	
Surgery for chronic ulcerative colitis.	6	83.3%	$X^2 = 8.361$ n = 1
Surgery for benign disease other than chronic ulcerative disease.	120	27.5%	p less than 0.005

did not develop complications (Table 3). The 105 patients who underwent surgery for malignant disease had a significantly ($p < 0.025$) greater complication rate (42%) than the 120 patients who underwent surgery for benign disease (28%) other than chronic ulcerative colitis. Surgery for chronic ulcerative colitis had a significantly higher complication rate than did surgery for other non-malignant disease (Table 4).

Several factors analyzed were found to have a statistically insignificant association with early postoperative complications in this series. When acute and chronic and free and contained are taken as a group, preoperative perforation is not associated with a significant increase in complication rate. Such coexisting diseases as diabetes mellitus, pulmonary diseases, cardiac disease, gastrointestinal diseases, renal disease, or urological disease, when diagnosed by traditional criteria, were not significantly associated with increased complication rate. However, newer hemodynamic studies may have greater predictive value in assessment of cardiac status.[9] Only the coexistence of hepatic disease was associated with a statistically greater rate of complications than cases without such coexisting disease (Table 5). Thirty-six cases had 45 other coexisting diseases. The complication rate in these 36 cases was 39%. Neither all resections nor resections done as emergencies had a significantly greater rate of complications than did non-resectional surgery. The mean age of patients with complications (60.32 ± 16.93 years) was not significantly different from that of patients without complications (59.14 ± 14.51 years).

The consequence of complications was analyzed in terms of duration of postoperative hospital stay. The mean duration of stay for patients with complications was 29.70 ± 23.77 days. The mean duration of stay for patients without complications was 13.22 ± 7.69 days. The difference was statistically significant ($p < 0.001$).

The cases in this series were placed in two groups according to the age of the operating surgeon. Patients operated upon by surgeons age 32 to 50 were placed in one group, Group Y. This comprised 158 cases. The cases of nineteen surgeons were in this group. The mean age of these surgeons was 43.4 ± 4.96 years. Patients operated upon by surgeons age 51–71 were placed in a second group, (Group O). This comprised 73 cases. The cases of 13 surgeons were in this group. The mean age of these surgeons was 59.6 ± 6.69 years. It was found that the complication rate for younger surgeons (Group Y) was almost twice that for older surgeons (Group O) and that this difference was statistically significant (Table 6). An attempt was made to determine whether other factors previously found to be related to increased complication rate were more commonly found in Group Y cases than Group O cases. Group Y surgeons operated upon significantly more emergency cases than did Group O surgeons (Table 7); however, significantly more Group O cases had hemoglobin less than 10 g than did Group Y cases (Table 8). In other categories previously examined and found related to complication rate, there was no significant difference in distribution between Group Y and Group O.

Discussion

In 6 of 13 deaths in this series, loop colostomy was the only operation performed. The operation itself probably had very little influence on the eventual outcome in such patients, who were usually gravely ill preoperatively. This may account for our mortality rate being slightly higher than the 3.5% reported by Judd[2] and by Beahrs.[2] However, it is comparable to the 5.8% mortality rate noted in Herter and Slanetz' series.[11] The overall complication rate of our series was 35.5%. It resulted from various types of colonic operations ranging from relatively minor procedures (e.g. loop colostomy, colotomy, closure of colostomy) to very extensive surgery (anterior resection and APR). It is higher than the overall morbidity of 24% reported by Schrock and

TABLE 3. *Complications and Duration of Operation*

	Total Cases	Mean Duration of Operation in Hours	
Complicated cases	82	2.97 ± 1.29	t = 3.51 n = 229
Uncomplicated cases	149	2.40 ± 1.11	p less than 0.001

TABLE 5. *Complications and Co-existing Hepatic Disease*

	Total Cases	Complication Rate	
Co-existing hepatic disease.	8	75%	$X^2 = 5.66$ n = 1
No co-existing hepatic disease.	223	34%	p less than 0.025

TABLE 6. *Complication Rate by Age of Surgeon*

	Age of Surgeon			Total	Complication	
	Range	Mean	Number	Cases	Rate	
Group Y	32-50	43.4 ± 4.96	19	158	41.8%	$X^2 = 8.37$ n = 1
Group 0	51-71	59.6 ± 6.69	13	73	21.9%	p less than 0.005

co-workers[19] in their series of 1703 cases of colonic anastomosis. However, it compares favorably with figures reported by Hedberg and Welch[10] for various types of colonic resections.

Emergency operations had a higher complication rate than elective procedures. Probably one important contributing cause was the inadequacy of bowel preparation in our emergency cases. In our series of emergency cases, we have noted wound infection occurred at the rate of 22%, exactly twice that of elective cases (11%). Mechanical cleansing of the colon has generally been accepted as of utmost importance in colonic surgery. However, Nichols and co-workers[16] have emphasized the value of appropriate intestinal antibiotics as well. Some controversy still surrounds the necessity of preoperative intestinal antibiotics. The main objection results from the serious complications of pseudomembranous (or staphylococcal) enterocolitis[11a] and reports of increased incidence of tumor cell implantation and growth at the colonic suture line after resection.[4] While the occurrence of the latter could not be assessed in our study, we have found that none of our patients receiving preoperative intestinal antibiotics has developed enterocolitis postoperatively.

On the other hand, Poth[17] and Cohn[5] both have shown that preoperative intestinal antibiotics significantly reduced incidence of wound infection and also protected colonic anastomosis in the presence of otherwise intolerable ischemia.

Other factors possibly related to higher overall complication rate in our emergency cases were increased frequency of preoperative obstruction, preoperative perforation (19 cases out of 45 in both) and preoperative hypoalbuminemia (12 cases out of 45). These conditions were considerably more frequent in emergency than in elective cases.

TABLE 7. *Distribution of Emergency Cases by Age of Surgeon*

	Total Cases	% of Total Cases Performed as Emergency	
Group Y (surgeons age 32–50)	158	23%	$X^2 = 4.94$ n = 1
Group 0 (surgeons age 51–71)	73	11%	p less than 0.046

TABLE 8. *Distribution of Anemic Patients by Age of Surgeon*

	Total Cases	% of Total Cases with Hemoglobin Less than 10 g	
Group Y (surgeons age 32–50)	156	6%	$X^2 = 6.81$ n = 1
Group 0 (surgeons age 51–71)	73	16%	p less than 0.014

In our series, we have noted a significant increase in overall complication rate if preoperative hemoglobin is less than 10 g% instead of 10 mg%. Most of the postoperative complications stem from poor healing of tissue. It has been known that the formation of collagen in the healing wound depends on hydroxylation of proline and this reaction requires atmospheric oxygen. Hunt and his co-workers[12] have demonstrated a steep fall in oxygen tension gradient in normal wounds. It is only logical to assume that any further reduction in the transportation of oxygen to these wounds, as in anemia, will depress oxygen supply below levels necessary for optimal healing in these tissues. Sandblom[18] had shown a 39.2% reduction in wound tensile strength in his anemic rabbits. Schrock and co-workers[19] in their series noted a twofold increase in anastomotic leakage rate in their anemic patients.

The high complication rate with hypoalbuminemia is probably again related to a decrease in healing ability in general. Findlay and Howes[7] have shown in rabbits that a 20% weight loss by starvation and protein depletion was accompanied by a delay in the initial appearance and growth of granulation tissue in healing wounds. Localio and co-workers[14] found a reduced formation of collagen in wounds with protein deprivation. In other experimental studies, it was further demonstrated that hypoalbuminemia not only causes a decrease in total tensile strength[6] but also a delay in the acquisition of this strength. In a clinical series, Alexander and Prudden[1] noted an increased incidence of wound dehiscence and eight times greater infection rate in patients with hypoalbuminemia. Anastomotic leakage is also more prone to occur because of an increase in collagen lysis coupled with a decrease in collagen synthesis.[13]

We have found that our patients with preoperative obstruction had a higher overall complication rate. This may be related to the susceptibility of these patients to malnutrition and fluid and electrolyte imbalance preoperatively. This condition also precludes optimal bowel preparation. With the combined effects of electrolyte imbalance and loss of colonic muscle tone prior to surgery, these preoperatively obstructed cases will tend to remain obstructed for longer periods postoperatively. It has also been noted, in the severely distended colon, that even if it is grossly intact, its thinned wall may be permeable to bacteria. All these may be related to their higher postoperative overall complication rate.

The overall complication rate was found higher in our patients having colonic surgery for malignant lesions than those for benign lesions. This seems to agree with Hedberg and Welch's[10] finding that total complication rate after sigmoid resection for diverticulitis was only one third of that for cancer. This may be related to the more extensive surgery performed for cancer. However, we cannot exclude the possibility that cancer patients tend to be more malnourished as a result of their decrease in dietary intake and production of proteolytic enzymes. It has been shown that many of them revealed a deficiency in serum protein and ascorbic acid. Glenn and Moore[8] have found the incidence of wound dehiscence in cancer patients was three times that of patients with benign lesions.

Our ulcerative colitis patients, however, showed a significantly higher complication rate than patients with other benign lesions. This may be related to the treatment with steroids commonly encountered in these patients. They are also more prone to be malnourished, anemic and have electrolyte abnormalities as a consequence of frequent bouts of bloody diarrhea. Findlay and Howes[7] have demonstrated the adverse effect of protein deficiency on wound healing with even low doses of cortisone.

Duration of operation and quantity of blood transfusion intraoperatively can be discussed together. We have found the overall complication rate is higher in cases with longer operating time and requiring a larger quantity of packed cells transfusion intraoperatively. It may again appear that a more extensive surgery was involved. However, the two factors probably reflect more on the hemodynamic status of the patient intraoperatively.

One of the undesirable side effects of anesthesia is the loss of physiologic compensatory mechanism to hypotension. Patients under general anesthesia are, therefore, more prone to suffer the deleterious effect of hypotension and this risk would be expected to increase in a prolonged operation. Packed cell transfusion intraoperatively was usually only given when there was evidence of hypotension due to excessive blood loss. Blood loss is also expected to be increased in a prolonged operation. Hence, the group of patients undergoing a longer procedure and requiring packed cell transfusion probably represented those with increased frequency and severity of intraoperative hypotension. This is accompanied by a decrease in tissue perfusion which may cause irreversible tissue damage and affect tissue healing ability generally. It is therefore logical to expect a higher complication rate in these patients postoperatively. Schrock and co-workers[19] reported a significantly increased rate of anastomotic leakage in patients with intraoperative hypotension, in those requiring 2 or 3 transfusions during the operation and in patients with operating time more than 5 hours.

The high complication rate with coexisting hepatic disease was not unexpected because these patients were usually debilitated, malnourished and had hypoalbuminemia.

It was found that the overall complication rate in cases performed by surgeons less than 50 years of age was significantly greater than in cases performed by those over 50. We also found that those significant factors mentioned above were not encountered more frequently in patients operated upon by the younger surgical group. We can only attribute our findings to probable superiority in experience, surgical judgment and techniques in our older surgical attending staff.

It is interesting to note that out of 13 deaths in our series, 9 cases were over the age of 65. It has been known that myocardial reserve is the major factor in determining operative survival of these patients. Gudwin *et al.*[9] have demonstrated from their hemodynamic studies, using an indicator dilution curve method, that it is possible to predict the myocardial reserve and hence, the operative survival of these patients. Mattingly[15] has stressed that mortality and morbidity rates are increased two to three times in patients with coronary disease.

We are suspicious that in many of our cases coexisting diseases might have been present but eluded our conventional means of evaluation. This may be a factor responsible in our finding of insignificant difference in complication rate between patients with certain coexisting diseases and those without.

In our cases with prophylactic antibiotics, we have found that their overall complication rate was not significantly different from those who did not receive them. This is in contrast to the apparent usefulness of prophylactic antibiotics found by others.[3,20] The lack of support from our series was probably due to the fact that only a minority of our cases received such measures and hence we were unable to provide a more meaningful comparison.

The lack of association of preoperative perforation with increased complication rate in this series is probably attributable to the inclusion together of both contained and free perforations and also chronic and acute perforations.

In our series, the overall complication rate was not significantly higher in both elective and emergency resection cases when compared with non-resection cases. It is true that in many of our gravely ill patients, only a minor procedure was attempted and they were prone to postoperative complications irrespective of whatever operations were performed. These cases may increase the overall complication rate in the non-resection group and made it comparable to that of elective or emergency resection group.

However, our findings may also imply that whenever the lumen of the colon is exposed in any type of colonic operation, the patient is subjected to the same risk in developing postoperative complications. Therefore, it behooves us to exercise the same quality of preoperative preparation, the same standard of surgical techniques and equal amount of postoperative care even in "minor" colonic procedures.

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Fecal Impaction Following Methadone Ingestion Simulating Acute Intestinal Obstruction

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A hitherto unreported clinical entity, namely fecal impaction following methadone ingestion simulating acute intestinal obstruction, is described. Five cases admitted to the Surgical Service of the Beth Israel Medical Center in New York City are discussed. The nature and pathogenesis of the obstruction are analyzed and a suggested method of managing these cases is presented. It is emphasized that with expansion and increasing acceptance of Methadone Maintenance Treatment Programs, the number of such cases will increase. It is thus important that physicians become aware of the existence of this syndrome since involvement in methadone maintenance may be a life-long commitment for persons involved, thus increasing the incidence of the complication. It is also imperative to avoid unnecessary, and possibly harmful surgical intervention in such cases.

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HEROIN ADDICTION has reached alarming proportions, particularly in the large metropolitan areas. In New York City alone, it is estimated that there are 150,000 addicts.[15] In the past, efforts to rehabilitate heroin addicts have met with dismal results. At Beth Israel Medical Center in New York City, methadone therapy was introduced for this purpose in 1964 by Dole and Nyswander and has been shown to be highly effective.[3,4,7] Although it substitutes one addiction for another, authorities on the subject are convinced that no other presently available therapy offers comparable promise.

At present in New York City, rapidly expanding Methadone Maintenance Treatment Programs (MMTP) are servicing 34,000 patients.[5] Of these, 6,400 are presently either under direct management at the Beth Israel Medical Center and Bernstein Institute or under supervision at other centers. Other areas of the country are now beginning to utilize this mode of therapy. In Massachusetts, enrollment in MMTP is only 900,[12] but it can be assumed that the development of treatment programs will follow changes in the distribution pattern of addiction. In addition, there are an unknown number of addicts who take the drug illicitly.

The Methadone Maintenance Treatment Program usually involves an induction period of six to seven weeks during which medical, psychiatric and social problems are evaluated and incorporated into the total treatment program. During this period tolerance almost invariably develops and the maintenance dose generally becomes fixed at about 100 mg per day. In studies emanating from programs at this institution,[6,11] it has been shown that tolerance to the autonomic and smooth muscle effects of methadone develops more slowly than tolerance to the sedative effects. At the clinical level this is manifested during the first year of treatment by excessive sweating and constipation. Physicians responsible for following patients in our clinics are aware of methadone's constipating tendency and frequently prescribe laxatives and stool softeners. With time, in chronic maintenance, these problems become infrequent. However, many physicians are not familiar with these "side actions." Moreover, the Medical Letter[13] warns that even seven years after its introduction, "the possibility remains of long term adverse effects that are still unrecognized, developing."

Two case reports have appeared in the literature[1,8,9] describing acute intestinal obstruction in drug addicts in which heroin is regarded as the responsible agent. We are presenting five cases in which chronic methadone users, not taking heroin, presented with acute intestinal obstruction indistinguishable on clinical grounds from the classical presentation of the entity.

Case Reports

Case 1 (J.C.): A 24-year-old Chinese male was admitted on December 17, 1973 with a two-week history of constipation, crampy abdominal pains for several days and two days of increasing abdominal distension. There was no vomiting, diarrhea and no previous history of constipation or sur-

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gery. The patient was a member of MMTP for six months with a current dose of 60 mg per day.

Examination revealed a markedly distended abdomen, generalized tenderness, no rebound tenderness and absence of bowel sounds. Rectal examination revealed soft stool in the ampulla. An abdominal x-ray study showed air-fluid levels throughout the small bowel with stool throughout the colon (Fig. 1).

The patient was given intravenous fluids, but nothing by mouth. He was treated with both high colonic enemas and Bisacodyl (Dulcolax) suppositories four times per day for three days, followed by oral cathartics.

He improved dramatically after passing large amounts of hard feces. A followup barium enema showed no bowel pathology.

Case 2 (P.W.): A 19-year-old white male presented on March 19, 1973 with a five-hour history of crampy abdominal pain and one episode of vomiting. His bowel movements had been regular and he denied constipation. There had been no previous surgery. He had been a member of MMTP for eight months with a maintenance dose of 80 mg of methadone per day.

Physical examination revealed a flat, non-tender abdomen, no scars, and hypoactive bowel sounds. Hard stool was felt on rectal examination. An abdominal x-ray film showed multiple air-fluid levels in small bowel and colon loaded with stool (Fig. 2).

He was treated initially with nasogastric suction and intravenous fluids. The next day high colonic enemas followed by cathartics were used. The patient improved immediately after passing large quantities of hard stool. He failed to return to the hospital for a barium enema.

Case 3 (J.M.): A 51-year-old Negro female was admitted on December 20, 1973 for alcohol detoxification and was being treated with paraldehyde in addition to her methadone. She developed abdominal cramps, distension and had four episodes of diarrhea the following day. Past history included an abdominal operation five years prior to admission (type?). She had attended a MMTP for three years and was maintained on 100 mg of methadone per day. Surgical consultation was sought. Examination revealed a distended, tender abdomen. Bowel sounds were hyperactive with rushes. Rectal examination revealed soft stool in the ampulla. An abdominal x-ray film showed multiple small bowel air-fluid levels (Fig. 3).

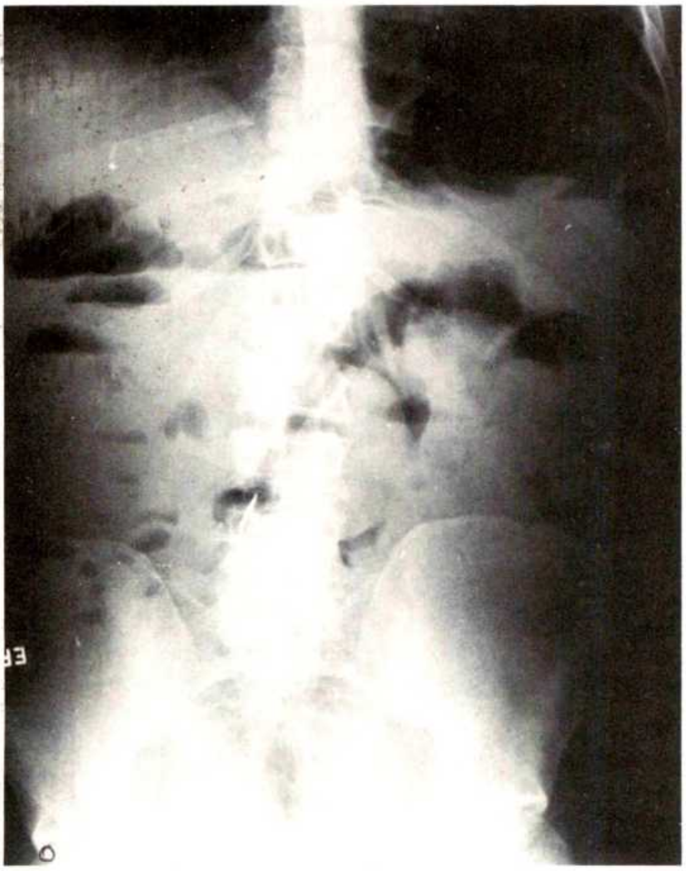

FIG. 1. (J.C.) Upright roentgenogram of the abdomen taken on admission to hospital and showing multiple air-fluid levels.

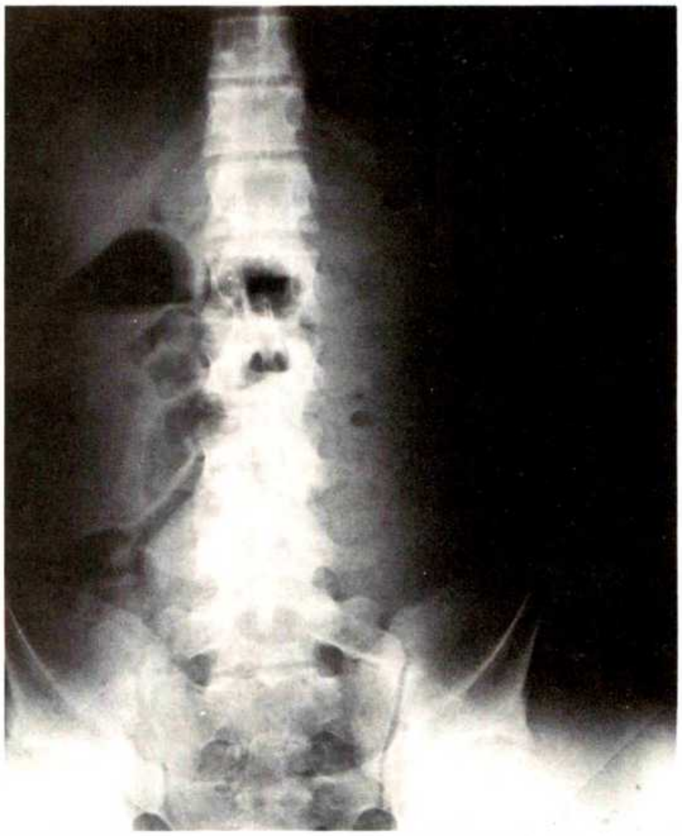

FIG. 2. (P.W.) Upright roentgenogram of the abdomen taken on admission to hospital and showing multiple air-fluid levels.

The patient was initially treated with intravenous fluids, given nothing by mouth, and decompression started using a Cantor Tube. Symptomatic improvement was noted and the tube was removed. The following day she again developed abdominal cramps and distension. She was treated with high colonic enemas and Bisacodyl suppositories four times per day which resulted in the passage of large amounts of stool. She improved clinically. An upper gastrointestinal series and barium enema performed prior to discharge from the hospital were normal.

Case 4 (H.P): A 30-year-old white female was admitted on October 20, 1973 with a one-day history of abdominal cramps, distension and obstipation for two days. Nausea was present, but no vomiting. Past history included previous operations for a duodenal ulcer, appendectomy, and ureterolithotomy. She had been a member of MMTP for one year, was maintained on 100 mg of methadone per day, and in addition was known to be addicted to barbiturates.

Examination on admission showed moderate abdominal tenderness, no abdominal guarding, and hypoactive bowel sounds. Rectal examination yielded soft brown stool. Abdominal x-ray studies showed large amounts of stool in the left colon with distended small bowel loops and air-fluid levels (Fig. 4).

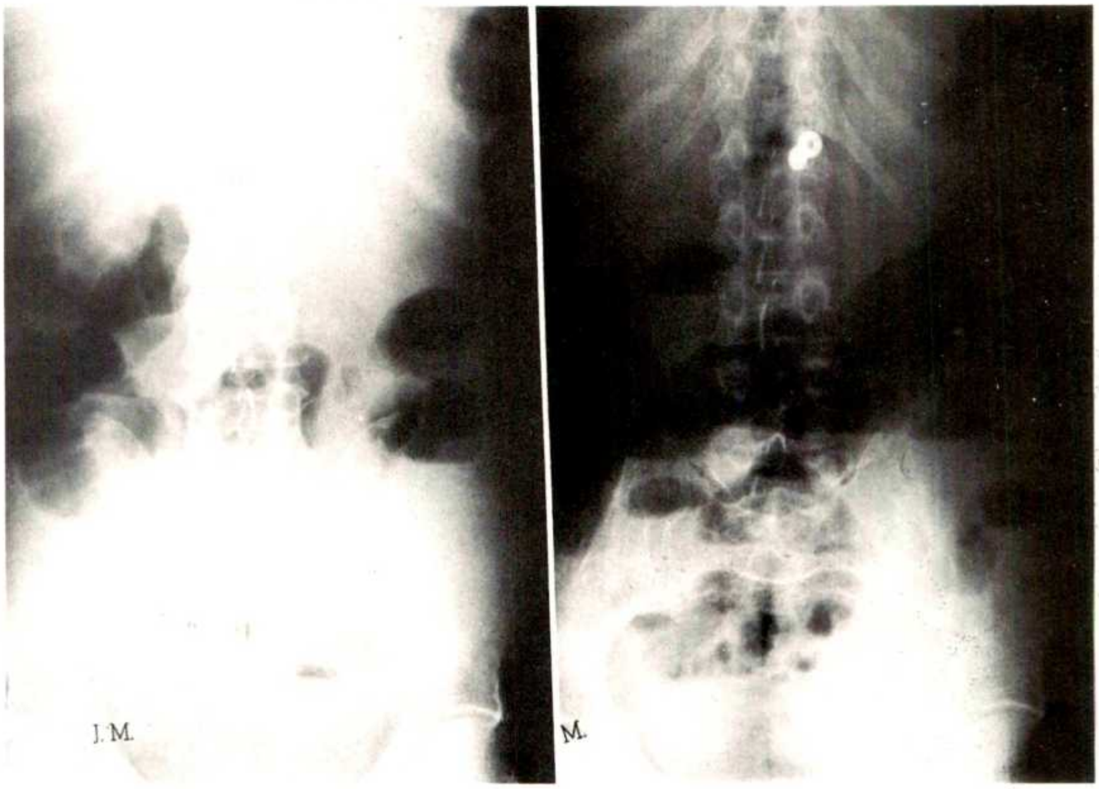

FIG. 3. (J.M.) Supine (left) and erect (right) roentgenogram of the abdomen, showing dilated small and large bowel loops and multiple air-fluid levels.

A Cantor Tube was inserted and intravenous fluids started. Good small bowel decompression was achieved. After two days the Cantor Tube was removed and copious bowel movements were obtained by means of high colonic enemas. A barium enema performed after discharge was normal.

Case 5 (W.C.): A 31-year-old Puerto Rican male was admitted to our Emergency Department and subsequently underwent an exploratory laparotomy for a stab wound of the abdomen on August 26, 1973. Operative findings included a laceration of the transverse colon and of the jejunum. The latter was oversewn and a transverse colostomy was performed for the former. The postoperative course included a wound infection which resolved satisfactorily, and the patient was discharged on the 21st postoperative day with the colostomy functioning well. Past history included a thoracotomy, also for a stab wound. The patient was a member of MMTP, taking 100 mg methadone daily and had been in the program for 3½ years.

Four days following the discharge he developed crampy abdominal pain, nausea and the colostomy ceased to function.

On examination, the abdomen was distended, diffusely tender and bowel sounds were hypoactive. The colostomy was not passing gas or fluid. A Cantor Tube was passed per os, a rectal tube placed through the colostomy, and intravenous fluids started. The patient began passing hard stool spontaneously via the colostomy with resolution of the symptoms. He underwent a colostomy closure and was discharged after having a barium enema which showed no pathology.

Discussion

Methadone hydrocholoride is a long-acting synthetic narcotic available for oral use. The analgesic effects are similar to those of morphine. Its effectiveness against heroin addiction results from its ability to block the euphoric effects of heroin and cravings for the opiate. The "highs" and the "sicks" of heroin abuse are eliminated. As a result of these methadone maintenance programs, our addict patient population has been shown to be capable of leading active and productive lives, with a significant percentage being gainfully employed and with crime involvement substantially reduced. Full cooperation is required for a patient to remain in the treatment program and the successful retention rate for 1972 was 76%.

Methadone and other morphine-like drugs have well-established effects on the gastrointestinal tract.[2,10,14] "Methadone causes relaxation of isolated intestine and inhibits the spasmogenic effect of acetyl choline and histamine on such preparations. However, in the intact, unanesthetized animal, methadone, like morphine, increases intestinal tone, diminishes the amplitude of contractions and produce a marked decrease in the propulsive activity of the intestine."[10] The resultant slower passage of the intestinal contents leads to an increased absorption of water and hence, hardened or inspissated feces. Therefore, on pharmacological grounds, it is reasonable to assume that chronic methadone usage can give rise to fecal impaction. It can also be assumed that, acting in a precipitating and aggravating capacity, the condition may progress, in extreme cases, to acute intestinal obstruction. This syndrome may be much more common than its absence from the literature indicates. In 1973, we, at Beth Israel Medical Center in New York City, admitted five such patients to the

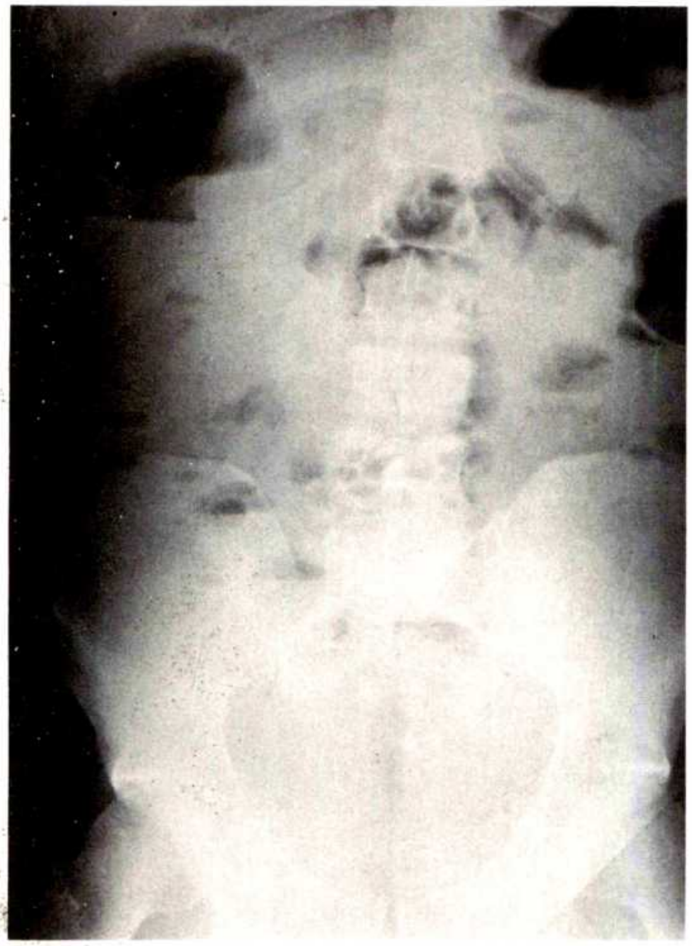

FIG. 4. (H.P.) Upright roentgenogram of the abdomen taken on admission to hospital and showing multiple air-fluid levels.

surgical service. This represented 4% of the methadone users admitted to the service for a variety of other surgical problems.

Symptoms and clinical findings in these patients may be indistinguishable from those of other patients seen with intestinal obstruction. Uniformly, they give a history of colicky abdominal pain, increasing abdominal distension and obstipation; occasionally they admit to previous constipation and in one instance the diarrheal pattern sometimes found with fecal impaction developed (Case #3).

On examination they may appear in great distress. Abdominal distension is a prominent feature and usually some tenderness is found. Although not occurring in the group reported here, a patient who has not received his daily methadone dose because of vomiting may display withdrawal manifestations, and these may further confuse the clinical picture. We have seen "rigidity" of the abdominal musculature and very marked abdominal tenderness in other methadone maintenance patients where such findings were part of the "withdrawal syndrome." Rectal examination often reveals soft stool in the rectal ampulla. In our series, four of the five patients had x-ray studies of the abdomen showing the classical pattern of intestinal obstruction, i.e., dilated loops of small bowel containing air-fluid levels.

However, the key to arriving at the proper diagnosis is the radiological observance of much fecal material in the colon. When this is paired with the clinical history of methadone maintenance, it should lead to the correct diagnosis. A cautionary note is in order lest the methadone effect represents only an aggravating factor which may mask some other pathological process causing mechanical obstruction. Moreover, as in all instances of intestinal obstruction, the clinician has a responsibility to think of and periodically re-evalute the patient in terms of bowel strangulation.

Proper treatment should begin with consideration of the correct diagnosis. Awareness of the syndrome in chronic methadone users is essential and may avoid unnecessary surgery in these patients.

A comprehensive and thorough history and physical examination must be undertaken. Any abnormalities in hydration or any electrolyte imbalance should be corrected. The patients are kept nil per mouth and fed intravenously. If vomiting and abdominal distension are marked, nasogastric drainage must be instituted. Vital signs must be closely monitored and important clinical and laboratory determinations made, such as temperature, leukocyte count, blood electrolytes, etc. In the early stages, re-assessment of the physical findings in the abdomen and other pertinent clinical determination should be pursued serially at appropriate intervals. Once the patient's general condition has stabilized and the possibility of bowel strangulation eliminated, colonic enemas at four to six hour intervals may be commenced. Bisacodyl suppositories may also be used. Only when the enemas begin to yield stool and there is clinical improvement, may oral cathartics be used. During this period of treatment the patient must receive his maintenance dose of methadone which is given parenterally.

The response to this mode of therapy is prompt and quite dramatic. As soon as the patient has passed stool, his condition improves rapidly.

Once the acute problem has been resolved, we suggest that all patients be adequately investigated, preferably prior to their discharge from the hospital. Studies should include sigmoidoscopy, a barium enema, an upper gastrointestinal series and small bowel series. Some of these patients are unreliable and others, once their symptoms are relieved, will not take time out for the indicated procedures after being sent home, hence the necessity for the full investigation while still in the hospital.

As methadone maintenance therapy becomes more widely used, and since methadone maintenance may be a lifetime program, we believe that the problem of acute intestinal obstruction secondary to the drug's use will be seen more frequently. We suspect that already some of these individuals may have been operated upon unnecessarily.

Addendum

Since submitting this paper for publication we have become aware of two patients with this syndrome at other institutions who were subjected to laparotomy at which no obstructing lesion was discovered.

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Primary Pulmonary Leiomyosarcoma:

Case Report and Review of Literature

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A case of primary leiomyosarcoma of the lung is added to the literature. Previously, 66 cases were documented. This is a case of a 55-year-old male, a pulmonary cripple for many years, with a collapsed left lower lobe found by roentgenogram, verified by bronchoscopy and bronchograms. Biopsy of lesion was reported as low grade leiomyosarcoma. Despite pulmonary function studies showing a vital capacity of 37% of predicted normal, a left pneumonectomy was preformed. Postoperatively, the patient had a tachycardia which gradually decreased in the next several months. Two months following operation pulmonary function studies were essentially unchanged from those made preoperatively. Arterial gas studies are presented pre and postoperatively.

LEIOMYOSARCOMA of the lung has been considered an extremely rare tumor in the past. In 1952, Johnson *et al.*[6] documented the first case successfully treated by pneumonectomy. There has been a gradual increase in the medical literature regarding this tumor since then. Havard and Hanburn[5] found 28 previously reported cases in 1960 and added an additional case. In 1965, Fadhli *et al.*[1] made a statistical review of 38 cases from the literature plus a case report. Guccion and Rosen[3] in 1972 reporting from the Arms Forces Institute of Pathology and the Veterans Administration Central Laboratory in Washington, D.C., reviewed 19 cases, three of which were previously reported, thus adding 16 cases. In all, 66 cases have been recorded to date.

This case is reported because of its successful conclusion in what was initially thought to be an irredeemable case surgically based on his history and pulmonary function studies. It represents the conversion of a "pulmonary cripple" to one capable of carrying on with everyday activities in a limited fashion.

Case Report

C.S., a 55-year-old white married male with a long history of asthma, bronchitis, emphysema and repeated bouts of pneumonia was admitted to Springfield Community Hospital on March 15, 1970, with chief complaint of shortness of breath on any type of exertion. Walking up one flight of stairs required three or four resting pauses. During the past two weeks, the symptoms had increased with associated wheezing and nonproductive cough. He had smoked since age nine and for many years consumed three to four packs of cigarettes per day. He stopped cigarettes 1½ years prior to admission, but smoked 16–18 cigars daily until June 1969, when he stopped completely.

Laboratory studies showed a Hgb. 17.5 gm/100 ml with a Hct. of 51%. WBC, differential, blood electrolytes and urine were essentially normal. Arterial blood gases: pH 7.384, pCO_2 48.3 mm, pO_2 75 mm, O_2 saturation 94%. Roentgenogram of chest showed a collapsed left lower lobe with compensatory emphysema of left upper lobe. The right lung was clear and overall the chest appeared somewhat emphysematous. Heart size was normal. Bronchoscopy revealed a polypoid type lesion occluding the left lower bronchus and a biopsy was taken. Because of his precarious respiratory balance, supravoltage radiation therapy was the only treatment considered initially until the pathology report was returned as leiomyosarcoma of relatively low grade malignancy.

Further evaluation was made. Pulmonary function studies showed vital capacity of 37% of predicted normal and on forced expiratory volume 1st Sec. 60%, 2nd Sec. 78%, 3rd Sec. 85%, with the maximum voluntary ventilation 26%. This was interpreted as a severe increase in airway resistance with severe loss of pulmonary compliance and an estimated 80% loss of pulmonary reserve. Bronchograms revealed an intraluminal lesion blocking the entire left lower lobe and extending into the left main stem bronchus and over into the major portion of the left upper lobe bronchus with only a very narrow irregular channel in the left upper lobe bronchus leading to normal size displaced bronchi distally (Fig. 1).

Because of the favorable prognosis of the leiomyosarcoma of low grade malignancy with surgical removal, an obvious trapped left lung and poor response of this type tumor to any type of radiation therapy, an exploratory thoracotomy was done through a left posterior lateral incision. The left lower lobe was completely atelectatic with compensatory emphysema without bullae of the upper lobe. There was a palpable mass in the inferior hilar region extending down into the lower lobe adjacent to the left lower lobe bronchus. Blood arterial gases were taken from the left pulmonary artery and repeated following its occlusion, in approximately 5 minutes. Specimen 1: pH 7.18, pCO_2 42 mm pO_2 45 mm. Specimen 11: pH 7.17, pCO_2 50.5 mm., pO_2 50 mm. A routine left pneumonectomy was carried out with dissection of three mediastinal lymph nodes as a separate specimen. An additional 1 cm of left stem bronchus was excised following inspection of the resected lung due to the proximity of the tumor to the cut edge. Frozen section of the separate bronchial specimen was negative for

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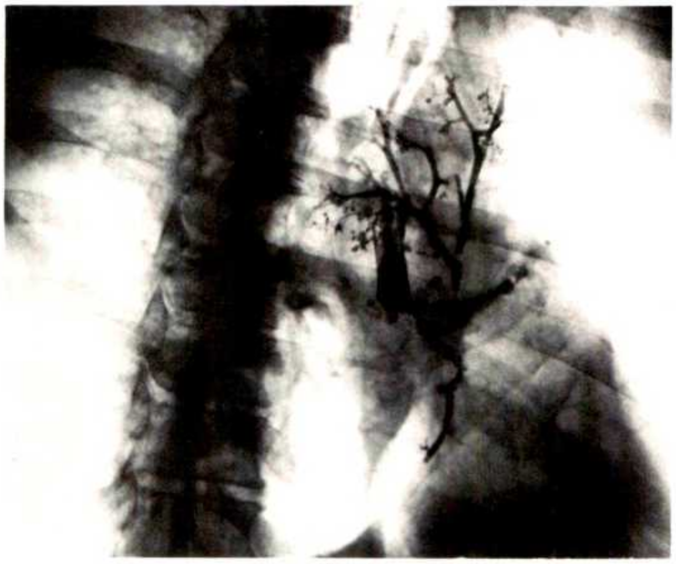

FIG. 1.

tumor. A tracheostomy was preformed at the conclusion of the procedure with the patient tolerating the operation well throughout.

Pathology report was leiomyosarcoma, moderately well differentiated arising from the lower lobe bronchus with metastases to the nearest peribronchial lymph node. The three mediastinal lymph nodes were negative for metastases.

Postoperatively, the patient did well, but because he developed an AV block and tachycardia, the digoxin dosage which he had been taking preoperatively was increased and then subsequently discontinued when it was felt that this might be a factor in the continuation of the tachycardia. He was placed on potassium which resulted in improvement. On the 9th postoperative day arterial gases were pH 7.472, pCO_2 34.5 mm pO_2 67.2 mm and O_2 saturation 93.5%. Improvement was gradual and he was discharged on the 21st post-operative day.

Two months following operation pulmonary function studies showed vital capacity of 40% of predicted normal. On forced expiratory volume 1st Sec. 60%, 2nd Sec. 73% and 3rd Sec. 86%. The maximum voluntary ventilation was 24% of predicted normal. This was interpreted as being essentially unchanged from preoperative studies and an estimated 50% reduction in breathing reserve. Arterial gas studies were normal with the pH 7.406, pCO_2 41.9 mm, pO_2 83.2 mm and O_2 saturation 95.3%.

Clinically, the patient has continued to do well, feeling better than he has for many years and capable of activities which were previously prohibitive. His pulse rate remains normal. He continues to take medication for his sinusitis and slight asthma plus an expectorant.

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Synovial Sarcoma

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Of 34 cases with synovial sarcoma, the five-year survival rate was 36%. A high local recurrence rate results when local excision is performed. Wide excision which may necessitate amputation is the treatment of choice. Prophylactic and even therapeutic node dissections are ineffective in increasing survival because of the disease. Evaluation of radiation therapy was impossible, although some patients obtained significant paliation. Adriamycin appears to have a tumoricidal effect and provided clinically significant responses in several patients.

SYNOVIAL SARCOMA is the term most commonly applied to an uncommon group of mesenchymal neoplasms arising from joints, bursae, and tendon sheaths. The unique diagnostic histological feature of these tumors is the coexistence of two neoplastic cellular elements; a cuboidal-columnar epithelial-like cell and an elongated spindle fibrosarcoma-like cell.

This report reviews our experience with 34 authenticated cases of synovial sarcoma treated at the Roswell Park Memorial Institute. Of the 34 patients, 6 and 13 were previously reported by Vincent[11] and Pickren[8] respectively.

Clinical and Pathological Features

Synovial sarcoma may occur at any age and equally in men and women, although most published reports indicate a slight preponderance for males. In this group of 23 males and 11 females, the age at the time of histologic diagnosis ranged from 10–78 years; with a majority of the cases occurring between the age of 15 and 50.

The tumor may develop in any site where there are tendons, joints, or bursae. Most published reports list the lower extremity and especially the knee as the most frequent anatomical site. In this group, 26 tumors or 76% occurred in the lower extremity and of these, 13 or 50% were associated with the knee.

Clinically, a majority of the tumors (19/34) presented as a painless, slowly enlarging mass. An exception were those patients with tumors arising in a functional element of the knee, where a majority presented as a painful knee months before a tumor was palpable.

The long clinical history and the problems of diagnosis are illustrated in the following brief case report.

Case Report

A.S., a 27 year old white male, fell and injured his left knee area in October of 1960. Intermittent pain prompted a tentative clinical diagnosis of a Baker's Cyst, although no mass was evident in the left popliteal area. During the next seven years, symptomatic relief of intermittent pain was obtained by application of heat to the knee. An increase in the pain during 1967 prompted removal of a cartilage from the left knee which did not provide relief of the pain. In March of 1968, a mass was detected and locally excised from the left popliteal space. Histologic study of this lesion demonstrated a synovial sarcoma. Thirty-nine days later, a left mid-thigh amputation was performed and the presence of residual disease in the surgical specimen was confirmed. The first recurrence (distant) was demonstrated by histological examination four years later following wedge excision of a 2 cm metastatic lesion in the lower lobe of the left lung. No further recurrences have been detected during the subsequent two years.

The anatomical site of the primary tumor may result in unusual presenting manifestations which occurred in one of our patients. Paralysis of the motor branch of the ulnar nerve, secondary to the development of a tumor in the palm of the hand, prompted search for medical care.

The duration of these tumors before definitive therapy varied from a maximum of 15 years to a minimum of four weeks. Twenty of the 34 patients sought medical attention within one year of the onset of symptoms. The interval from the time of biopsy to definitive surgical treatment ranged 7–46 days, with an average of 23 days.

Measurements of the primary tumor at the time of

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diagnosis were documented in 23 cases; the smallest tumor was 3 × 3 cm and the largest tumor was 16 × 23 cm. The average diameter of the tumor was 8 × 9 cm. This reflects the painlessness and the lack of interference with function.

The gross appearance of the tumor could be evaluated from clinical notes or personal observations in 15 of the 34 patients. A striking feature was psuedo-encapsulation which was misleading since simple enucleation invariably resulted in local recurrence.

Roentgenographic studies were not helpful in the diagnosis, although angiographic studies may be helpful in delineating the size, extent and infiltration of the tumor.

Thirteen patients underwent surgical procedures which provided tissue of lymph node bearing areas for histological study. The clinical impression versus the histological examination of these nodes is summarized in Table 1. Three patients with clinically positive nodes were found to be negative for tumor invasion on histological examination. Six patients had clinically negative nodes confirmed by histological study. Four patients with advanced disease had clinically positive nodes and on histological examination were found to be invaded by tumor.

Surgical procedures (local excision, wide excision, and/or amputation) were performed upon 18 additional patients without node dissections. During the followup period, 72% (13/18) developed distant metastasis and 2/18 developed local recurrences without lymph node invasion.

Treatment and Results

Table 2 summarizes the followup of these 34 patients with synovial sarcoma. Six patients were treated initially following biopsies by supra-radical amputations (forequarter 2 and hindquarter 4) and the first recurrence was distant in all six patients, less than one year in five patients and one year and six months in the remaining patient. Three patients died of metastatic disease at eight months; two years; and four years eight months. Three patients are living (nine months, 12 months, and 30 months) with pulmonary metastasis and two of the three patients have responded to chemotherapy, Adriamycin and Dimethyl Triazeno Imidazole Carboxamide.[4] Fourteen patients were treated initially by biopsy, enucleation, or local excision for diagnosis followed by amputation, and in addition two of the 14 patients had an incontinuity dissection of the regional lymph node bearing area. Ten patients had pulmonary metastasis detected within a period of 10 months to as long as five years and three of the 10 patients were

TABLE 1. *Summary of Clinical vs. Histological Study of Lymph Nodes*

No. of Pts.	Clinically Positive	Clinically Negative	Histological Positive	Histological Negative
3	3			3
6		6		6
4	4		4	

TABLE 2. *Clinical Resumé of Treatment: 34 Patients with Synovial Sarcoma*

Surgical Procedure	No. Pts.	First Recurrence Local	First Recurrence Dist.	Additional Recurrences Local	Additional Recurrences Dist.	Other Treatment Surg	Other Treatment Chemo.	Other Treatment Rad.	Living NED <5 yrs.	Living NED >5 yrs.	Living c̄ Disease <5 yrs.	Living c̄ Disease >5 yrs.	Died Disease <5 yrs.	Died Disease >5 yrs
L. E. Biopsy and Forequarter or Hindquarter Amputation	6		6		1	2	4	1			3		3	
Biopsy or L. E. and Immediate Amputation	14		10		1	2	7	5	1	3*	1		8	1
L. E. and W. E. or W. E.	4	2		1	1	1	2	2	1	1	1			1
L. E.	2	2		1	1	2	2	1		1			1	
L.E. and W. E. Postop. Chemo.	2		1			1			1				1	
Biopsy or L. E. Radiation	2	1			1			1		1†			1	
Biopsy (distant disease) Palliative Rx	4					1	3	3					4	

* One > 10 yrs. One > 17 yrs.
† Living, No Disease 23 years.
L. E. = Local Excision.
W. E. = Wide Excision.
NED = No Evidence of Disease.

within less than one year. In addition to the pulmonary metastasis, one of the 10 patients developed a recurrence at 15 months in the amputated site of the limb, distal to the in-continuity groin dissection. Of these 14 patients, eight died with progressive disease in less than five years, and one patient at seven years. Five patients are living; two less than five years, one free of disease, and one with disease, and three patients are free of disease at 10 years seven months; five years four months; and 17 years, respectively.

In summary, of the 20 patients with amputations (6 supraradical and 14 major), 16 developed pulmonary metastasis and of these, eight patients or 50% had detectable metastasis within one year.

A local excision followed by a wide re-excision of the primary lesion was performed in four patients. A local recurrence was observed in two patients within two years. Three patients are living, two less than five years (one with and one without disease) and one patient is free of disease for six years. One patient died at eight years eight months with progression of disease.

Initially, only a local excision of the primary lesion was performed in two patients and local recurrences were observed in both patients within seven months. One of these patients had an above-the-elbow amputation for the local recurrence in the hand. Lung metastasis were detected within two years and a regression of all lesions by more than 75% for nine months was observed following chemotherapy with Adriamycin. Unfortunately, while on chemotherapy there was progression of disease and death with a survival time of three years six months from the time of initial diagnosis. The second patient was treated by an above-the-elbow amputation for the first local recurrence in the primary site of the elbow. Within 10 months a second local recurrence in the amputated site was treated by combined wide local excision, postoperative radiation (5000 rads) to the stump, and systemic chemotherapy (Vincristine and Cytoxan). This patient is living free of disease at five years six months from initial diagnosis. This recurrence in the site of the amputation raises the question in regard to the optimum site a limb should be sacrificed proximal to the primary tumor for removal of all tissue which may contain tumor cells extending along fascial planes.

Two patients were treated by local excision followed by wide excision and chemotherapy (Vincristine-Cytoxan and Nitrogen Mustard). One patient is living (two years six months) free of disease and the other patient died with progression of pulmonary metastasis at four years two months.

The primary lesion in one patient was treated by local excision followed by 4500 rads of radiation therapy. This patient has remained free of disease for 23 years. Another patient with a large fixed tumor mass of the left shoulder supraclavicular area was treated, following only biopsy for diagnosis, with a total tumor dose of 10,000 rads of radiation therapy (5000 rads external and 5000 rads by radium seeds). Initially, the patient had refused a forequarter amputation. The radiation therapy provided a 30% reduction in the fixed tumor mass, thus converting the primary lesion into a locally resectable lesion. Unfortunately, a local recurrence at the primary site was detected within six months with progression and the appearance of distant metastases and death at two years five months.

Four patients were surgically incurable with pulmonary metastasis at the initial examination. These four patients received palliative treatment (surgery, radiation, chemotherapy) and all died within one year and seven months.

The antitumor effect of 14 chemotherapy agents administered as either a single agent or in various combinations for disseminated disease in 23 patients is summarized in Table 3. It is noteworthy that an objective response followed Adriamycin therapy in four of seven patients. One of these four patients has had a reduction in size of tumor lesions greater than 75% without the appearance of new lesions for more than three years.

Eight patients are living with or without disease for a period less than five years; four patients were inoperable when first seen. Thus, 12 patients in this series of 34 patients are not included in the five-year survival. Of the remaining 22 patients, eight of 36% were living free of disease at five years. Subsequently, two of these eight patients had pulmonary metastasis detected at seven years which was followed by progression and death.

Comment

Synovial sarcomas present unique problems of diagnosis and therapy. This malignancy is characterized by local recurrences from direct extension for long distances along tissue planes and distant spread by way of the vascular system, thus resembling the biological characteristics of other connective tissue sarcomas. The pattern of the fatal distant metastasis reflect two factors: 1) vascular dissemination; and 2) possible predilection sites which may be

TABLE 3. *Response Following Non-surgical Treatment of Disseminated Disease*

Type of Therapy	No. Pts.	Objective Response*
Chemotherapy Individual Agents (Hydroxyurea, Mitomycin C, 5-FU Cytoxan, Vincristine, Methotrexate, Alkaran, Dactinomycin, Nitrogen Mustard, Thio Tepa, Thiocarzolamide, Cytosine Arabinoside, N^6Benzyladenoside)	16	0
Adriamycin†	7	4
Immune Therapy	6	0

* Regression of lesions without new lesions of 50% for 2 or more months.

† Combination with DTIC in 3 patients, no evidence of effect.

"favorable soil" for this tumor, that is; pleura, lung, diaphragm and pericardium.

The prognosis of synovial sarcoma is generally poor and the five-year survival of 36% in this series of patients is similar to other reports.[1,3,10] MacKenzie[6] reported a 51% disease free, five-year survival in a series of 49 patients. This increase in survival was attributed, in part to a shorter history interval before treatment than reported in other series. Pack and Ariel[7] reported a 23.5% five-year survival in a series of 60 cases and in this series, those patients presenting with pain had a 38.4%, five-year survival. In our series, the five-year survival in those patients presenting with pain was 44%; therefore, both series of cases may indicate an earlier search for medical care and earlier surgical intervention because of pain.

The prognosis appears to be related to two critical factors; namely, 1) that these tumors tend to have a long natural history and thus surgical intervention is performed late in the course of the disease; and 2) the continued attempts of conservative surgery for a grossly benign-appearing, in many instances "encapsulated," lesion which possesses a high malignant potential.

The reported incidence of local recurrences following local excisions of 28% to 92%[2,6] emphasizes the failure of conservative procedures. In this study, residual tumor was detected histologically in specimens from five of nine patients who had wide reexcision of recent locally excised lesions. Surgical treatment of synovial sarcoma must include early detection, wide excision of the lesion including amputation when those areas in which the underlying structures do not permit an adequate excision.

The reported incidence of metastasis to regional lymph nodes of 12 to 37%,[1,5,9,12] has prompted some surgeons to recommend node dissections as an integral part of the initial surgical procedure. It is our observation that growth of tumor tissue in lymph nodes is usually a late phenomenon and that benefit from therapeutic node dissections is limited.

The value of radiation therapy used as the only therapy, or in combination with surgery cannot be evaluated from our series and other reported studies, because of small numbers of patients that are subdivided further by different methods of radiation therapy. Various degrees of tumor regression and pain relief were observed in several of our patients following various tumoricidal doses of radiation. One patient had residual viable tumor after exposure to a minimum of 10,000 rads. Despite a general consensus that soft tissue sarcomas are radioresistant, protocol studies using large tumoricidal dosages (6,000–10,000 rads) may provide information as to the effectiveness of improving survival alone or in combination with surgery.

Most chemotherapeutic agents have been ineffective, but the antitumor effect of Adriamycin is encouraging and further studies of this agent in combination with surgery and/or radiation for treatment of the primary lesion and for disseminated disease is indicated.

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Results of Conservative Treatment of Breast Cancer at Ten and 15 Years

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The ten-year survival of patients at the Cleveland Clinic treated by operations less than radical mastectomy was 45% compared with 43% in identically staged patients of the "National Cancer Registry" treated predominantly by radical mastectomy. The five and ten-year survival rates of patients treated by simple operations was higher than that of a similar group of patients treated by radical operations, but at 15 years there was no difference. The late deaths from cancer in the patients treated conservatively occurred in patients with favorably staged cancers who never had local recurrences and most of whom had no involvement of nodes. The incidence of local recurrence was no higher after simple operations than after the radical procedure. The ten-year incidences of local recurrence and of death from cancer were the same after partial mastectomy as after total mastectomy. It is pointed out that differences in staging the cancers and in reporting the survival rates invalidate comparisons of results from different institutions. The figures presented suggest that conservative operations and radical operations give the same survival rates at ten and at 15 years.

PROPONENTS of radical mastectomy have criticized the results of lesser operations on the basis of an inferior ten-year survival rate. The purpose of this article is to compare ten- and 15-year survival rates following operations less than radical mastectomy with those of patients treated predominantly by the standard radical operation.

Material

All patients with Manchester Stages I and II cancers seen at the Cleveland Clinic in the years 1957 through 1963 were included. None were excluded because of age or disability.

There were 355 patients with Stages I and II cancers in a total of 454 patients with previously untreated breast cancer seen in all departments of the Cleveland Clinic. Stages III and IV included patients with distant or supraclivicular metastasis, fixation of axillary nodes, edema of arm, inflammatory carcinoma, or satellite skin nodules distant from the cancer. Regardless of the size of tumor or of the nodes, the patients were still classified as operable Stages I and II unless they had one or more of the above signs. The stage of the cancer, the histologic type, the treatment given, and the proportion of patients followed are shown in Table 1.

Cobalt teletherapy was used chiefly for the definitive treatment of patients with such extensive metastases that it was decided to treat the axilla by radiation rather than by surgery. In addition, 13% of the patients with clinical Stage I cancer were irradiated prophylactically. Most of these were selected for radiation treatment because the tumors were large or unfavorable.*

The treatment employed induced almost no morbidity. Fewer than 1% of the patients had infections or sloughs. Significant arm edema or limitation of motion of the shoulder occurred in only one patient, after irradiation. All but six of the patients were followed for ten years. Three that were lost to followup between six and eight years had no nodes involved, were well when last seen, but have been counted as dead.

Results at Five and Ten Years

At five years 72% of the operable Stages I and II patients were living, and at ten years, 45% were living, counting the six lost patients as dead.

These results are remarkably similar to those published by the National Institutes of Health in "End Results in Can-

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* Although tumor did not later appear in the nodes of any of the irradiated Stage I patients, it is likely that a third of this group of 17 were originally true Stage II and had involvement of nodes. This means that at least five patients would have to be added to Stage II, increasing the proportion of true Stage II cancers to 47%.

TABLE 1. *Stage (Manchester), Type of Treatment and Followup of All Cleveland Clinic Patients with Previously Untreated Breast Cancer 1957–1963 (Inclusive)*

	No.	%
Total patients	454	
Operable Stages I and II	355	
True Stage I	189/355	53
True Stage II	166/355	47
Invasive cancer	342/355	96
Modified radical mastectomy*	144/355	41
Simple mastectomy†	204/355	58
Radical mastectomy	4/355	1
Cobalt, postoperative	78/355	22
Lost to followup 5 years	2/355	0.7
Lost to followup 10 years	6/355	2

* Included are seven patients who had partial mastectomy and axillary dissection

† Included are 38 patients who had partial mastectomy without axillary dissection.

cer," Report No. 4, 1972. The figures were obtained from the Cancer Registries of California, Connecticut, and Massachusetts, and from six university hospitals. Nearly all of them were treated by radical mastectomy (Table 2).

Evidence that the stage of the disease in the two groups was similar is furnished by the fact that the proportions of patients with Stage I cancers were the same, as were also the survival rates of the patients who were classified as inoperable (Stages III and IV). Fourteen per cent of the Cleveland Clinic Stages III and IV patients survived five years as compared with 12% of those from the Registry.

There are two possible interpretations of these figures. The first is that, despite the apparent similarity in staging, the patients seen at the Cleveland Clinic were for some reason in a more favorable stage of the disease. This is manifested by the higher survival rate of the Clinic patients at five years. But the fact that the ten-year survival rates were identical would imply that the long-range results of conservative operations were inferior to those of radical mastectomy.

In the second interpretation, it is assumed that in the two groups the stages of the cancers were indeed the same, as evidenced by the identical staging of the patients with operable cancers and by the similar rates of survival of those with inoperable cancers. This interpretation is supported by the identical ten-year survival rates of the two groups, and suggests the possibility that the lower five-year survival rate in the Registry series was the result of impariment of immunity by radical surgery and/or radiation.

Effects of the Type of Operation on Long-term Survival

Delayed Axillary Dissection for Occult Cancer in Nodes Gave as Good Results as Immediate Dissection

We have seen an advantage to simple operations at five years, but none at ten years. If this result was caused by failure of the simple operations to control the cancer locally it should manifest this failure by a significant incidence of recurrence locally, or in the axillary nodes.

During 1957 through 1962, some of the Clinic surgeons were routinely performing modified radical mastectomies, even where there was no palpable involvement of nodes, and others in the same circumstance were doing only a simple removal of the breast. During this period 28 patients with no evidence of involvement of nodes either clinically or at the time of axillary exploration were treated by mastectomy and axillary dissection, and the pathologist found occult cancer present in the nodes. Another 24 patients with occult cancer in nodes were treated by mastectomy only, without axillary dissection or radiation; but within the next five years all were found to have evidence of axillary metastasis. Twenty-one were treated by delayed axillary dissection and three by delayed cobalt teletherapy. There was no significant difference in the ten-year survival rates of the two groups (Table 3).

The small difference in five- and ten-year survival rates (11% in favor of the simple operations at five years and 4% at ten years) can be explained by selection, for the average diameter of the cancers treated by modified radical mastectomy was 3.1 cm compared to 2.1 cm for those treated by simple operations.

There was less difference than one would anticipate in the extent of nodal involvement in the two groups. The three patients treated by simple mastectomy and delayed cobalt teletherapy were so treated because the nodal involvement seemed extensive. Assuming that each had more than three nodes involved, we find that 11 (39%) of the 28 patients treated by immediate axillary dissection had more than three involved nodes compared to 16 (33%) of those treated initially by simple operations. Therefore, from the standpoint of the extent of nodal involvement, which is the most important factor in prognosis, the two groups were matched. It seems that there is little or no advantage in prophylac-

TABLE 2. *Comparison of Staging and Survival of Patients with Operable (Manchester Stages I and II) Cancer in National Cancer Registry and Cleveland Clinic Series*

	Cancer Registry Radical Operations (1955–1964, incl.) %	Cleveland Clinic Simple and Modified Radical (1957–1963, incl.) %
Proportion of patients in Stage I	53	53
Proportion of patients in Stage II	47	47
Stages III and IV, lived five years	12	14
Stages I and II, lived five years	61	71 (252/355)
Stages I and II, lived ten years	42.8	45* (158/355)

* Three patients with Stage I cancer, well six to eight years, were lost to followup and counted as dead.

TABLE 3. *Results of Treatments in Patients with Occult Cancer in Nodes (Operative Stage I True Stage II)*

	Immediate Modified Radical Mastectomy*	Simple Mastectomy Axillary Dissection Later. No radiation†
Lived five years	18/28 = 64%	18/24 = 75%
Lived ten years	8/28 = 29%	8/24 = 33%

* Eleven of 28 had three or more nodes involved (39%).
† Eight of 24 had three or more nodes involved (33%).

tic dissection of axillary nodes that contain occult deposits of cancer, for these nodes can still be treated successfully when the metastasis appears.

The Incidence of Local Recurrence was no Higher After Conservative Operations than After Radical Ones

A second consideration in determining whether radical operations are more curative than simple ones is the incidence of local recurrence. It is hard to see how a radical operation could be considered more curative than a simple one, if after the simple operation there is no higher incidence of local recurrence in scar, breast, or axillary nodes.

As shown above, the first recurrence in nodes after a simple operation does not adversely affect survival, provided that the involved nodes are removed as soon as they become palpable. However, recurrence in the operative field after either surgery or radiation would have to be considered a serious complication associated with a lower rate of survival. The incidence of local recurrence at ten years was 20/355 (5.6%). Since this is lower than the 10% to 15% incidence of local recurrence that is usually reported after radical mastectomy, it appears that local recurrence could not be a factor in lowering the ten-year survival rate after simple operations.[*]

The Ten-year Survival Rate and the Incidence of Local Recurrence After Partial Mastectomy was the Same as After Total Mastectomy

Since only 45 of the 355 operations were partial mastectomies (13%), it is unlikely that inferior end results following partial mastectomy could have had a significant effect in lowering the ten-year survival rate of the patients in this series.

Moreover, a randomized matched-pair study (matched for type of cancer, size of cancer and involvement of nodes) showed no significant difference in the ten-year survival rates of patients treated by partial as compared with total mastectomy. Because there was selection toward treating older patients by partial mastectomy, the average age and the incidence of death from causes other than cancer was higher in the patients treated by partial mastectomy. But the incidence of death from cancer was the same in both groups (Table 4).

Late Deaths After Conservative Operations Were not Associated with Local Recurrences

The foregoing ten-year report included only the patients treated in the years 1957 through 1962. During that period almost all patients having axillary dissections were treated by modified radical mastectomies. However, radical mastectomy was not abandoned at the Cleveland Clinic until 1958, so that during the years 1955, 1956, and 1957, 25% of the radical operations were still of the conventional type with removal of muscles. It is therefore interesting to compare the long-term results of treatment by modified-radical or radical mastectomy during this period, often followed by radiation, with those following simple operations in which no attempt was made to remove the nodes and radiation was less frequently employed. All patients had invasive cancer.

The staging of the two groups is not comparable, because the patients treated by radical or modified radical

TABLE 4. *Matched* Pair Study (42 Cases) 1957 Through 1963 (Incl.) Followed for Ten Years*

	Partial Mastectomy	%	Total Mastectomy	%
Average Size Tumor (matched)	2.1 cm		2.1 cm	
Proportion with Nodes Involved (Matched)	19/42	45	19/42	45
Average Number of Involved Nodes	5		4	
Median Number of Involved Nodes	2		1	
Invasive Cancer (matched)	42/42		42/42	
Special Types	2 mucinous		1 papillary	
Average Age	57 yr		51 yr	
Axillary Dissection	9/42 (3-delayed)		26/42	
Cobalt, Postoperative	11/42		17/42	
Local Recurrence	3/42	7	5/42	12
Lived Five Years	31/42	74	26/42	62
Lived Ten Years	17/42	40	21/42	50
Died Ten Years, Causes Other Than Cancer	9/42	21	5/42	12
Cause of Death, Unknown	2/42	5	0/42	0
Died of Cancer, Less Than Ten Years	14/42	34	16/42	38

* Partial mastectomy vs. Total Mastectomy; matched for: 1) invasive cancer; 2) size of cancer; and 3) involvement of nodes.

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[*] If the axilla had not been treated by surgery or irradiation, the first appearance of cancer in axillary nodes was not counted as a local recurrence. Any subsequent recurrence was so considered.

operations tended to have moderately advanced cancers, whereas those treated by simple operations with or without radiation tended to have both the earliest and the most advanced ones. There was also some selection in respect to age, the average age of the patients treated by simple operations being three years more than that of the patients treated by radical operations.

At five years, and even more so at ten years, there was a considerably higher survival rate in the patients treated conservatively. Between ten and 15 years, however, this advantage was lost, and the survival rates became the same (Fig. 1).

During the period ten to 15 years after treatment, 15 of the 69 patients who had been treated by simple operations died, eight of cancer and seven of other causes.

During the same period only four of the 62 patients treated by radical or modified radical mastectomy died, all of causes other than cancer. Thus in the period ten to 17 years after operation, 12% of the patients treated by simple operations died of cancer, compared to none of the 62 who were treated by radical operations. Does this mean that the simple operations gave inferior long-term results? Or does it mean that the long-term results were the same, but the short-term results were better after the simple operations? The answer lies in an analysis of the type of treatment and of the course of the disease in the patients who died late.

One of the most important supports for the concept that conservative treatment gives long-range results comparable to those following radical operations is the fact that all of the late deaths in patients treated by conservative operations were in patients who had never had any local recurrence of cancer.

Five of the eight patients treated by simple operations who died of cancer between ten and 15 years later had true Stage I cancers. Two more had had immediate axillary dissection for involved nodes. Radical operations could not have extended their periods of survival. Seven more died of causes other than cancer and without recurrence. Again a radical operation could not have affected their course. One patient, treated by simple mastectomy, had a late appearance of cancer in an axillary node, but there was never any local recurrence after delayed axillary dissection. Therefore, it seems unlikely that in this group of cases the increased incidence of death between ten and 15 years was the result of a relative failure of the conservative treatment.

Discussion

There are several reports of ten-year survival rates of patients with breast cancer treated by radical mastectomy that are as much as 18% higher than those reported from the Cleveland Clinic or by most surgeons who treat breast cancer by standard radical mastectomy. On careful reading of

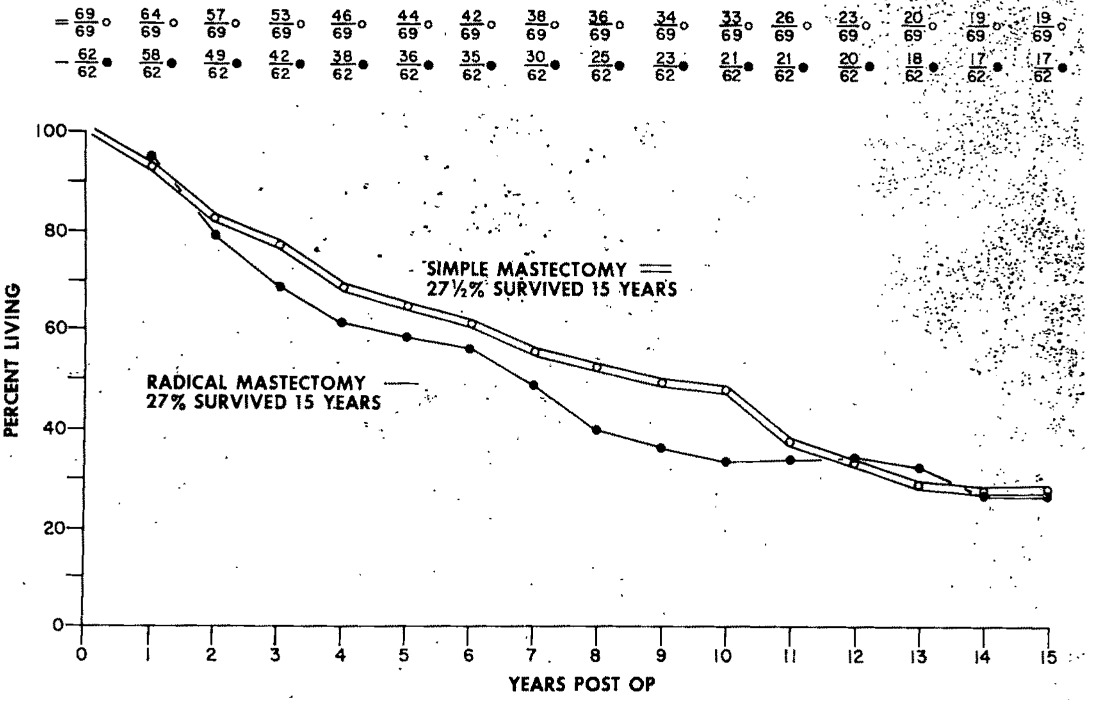

FIG. 1. Comparison of survival after simple and radical mastectomies at the Cleveland Clinic, 1955–1957. Radical mastectomy includes modified radical. Simple mastectomy includes partial mastectomy.

SIMPLE DIED OF Ca 10 TO 15 YRS 7/33 : D.O.C. 7/33
RADICAL DIED OF Ca 10 TO 15 YRS 0/21 : D.O.C. 4/21

1955, 1956, 1957 ALL OPERABLE STAGE I AND II CANCERS
(NON-INVASIVE INTRADUCT CANCERS EXCLUDED)

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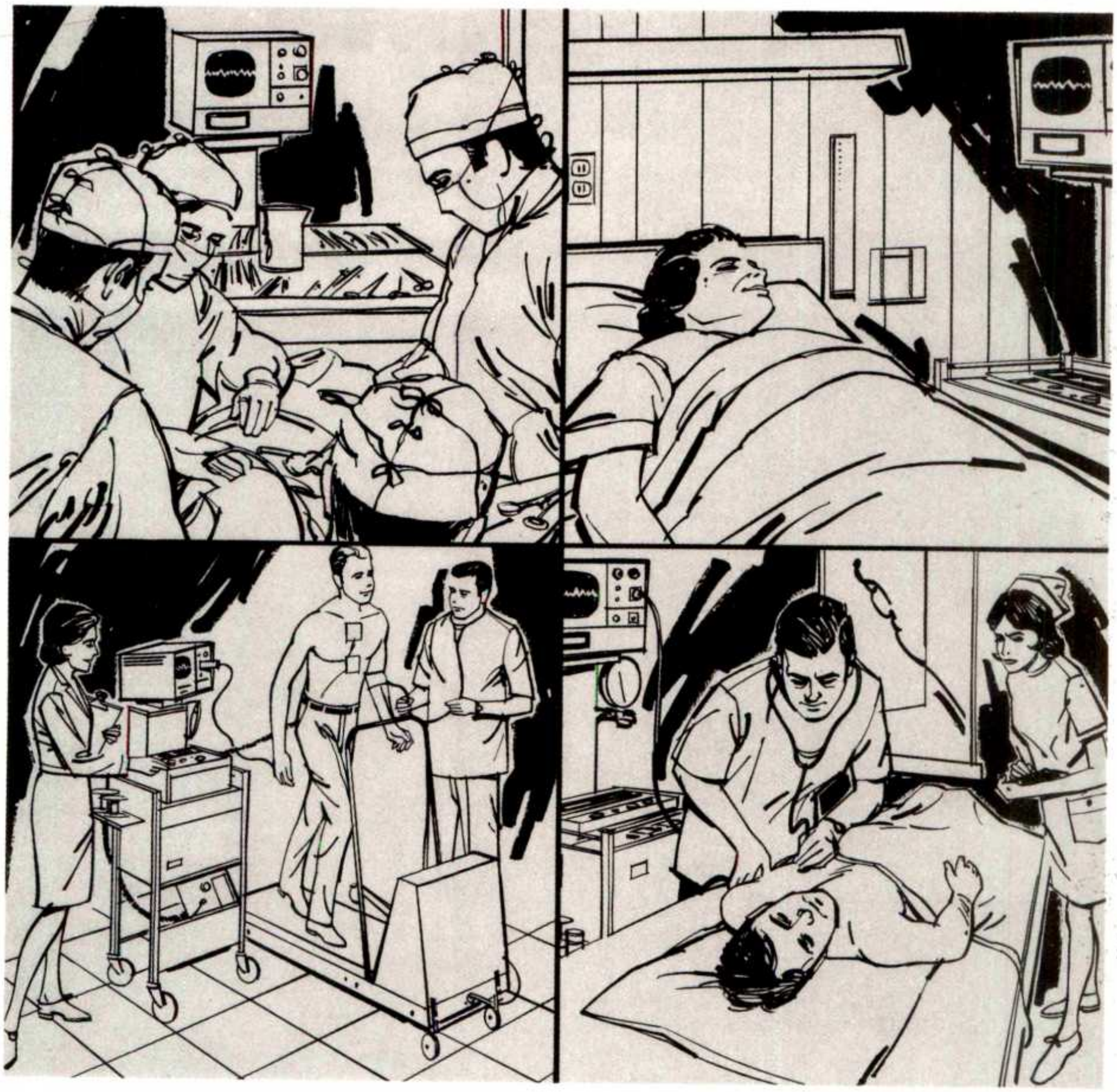
these, however, one finds that one or more of the following qualifying factors are present: 1) The report includes only patients selected for treatment by radical mastectomy. 2) The figures quote relative or definitive survival rates in which a correction is made for patients dying of causes other than cancer. 3) The patients are staged in such a way as to exclude the advanced Stage II cancers that are included in the Cleveland Clinic's Manchester staging. 4) The proportion of noninvasive (intraduct or lobular in situ) cancers is not stated. 5) The patients come from a referred private practice and do not represent an overall institutional experience, hence many small carcinomas may be diagnosed early.

In this study, comparing the results of conservative operations at the Cleveland Clinic with those of radical ones reported in the National Cancer Registry, long-term survival after treatment of cancer of the breast appears to depend more on the original state of the disease than on whether radical or conservative treatment was given. Although the numbers are too small to be of statistical significance. The short-term survival seems to be slightly shortened by radical treatment.

Conclusions

It is important to evaluate the literature carefully before concluding that one form of treatment of breast cancer has any long-range advantage over another. The figures presented here suggest that conservative operations and radical operations give the same rate of survival at ten and at 15 years.



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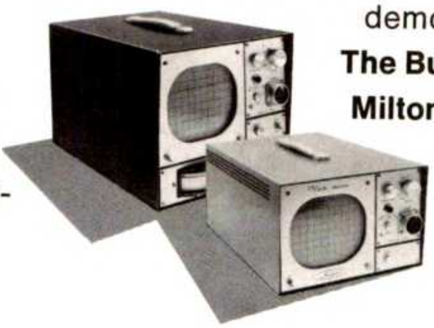

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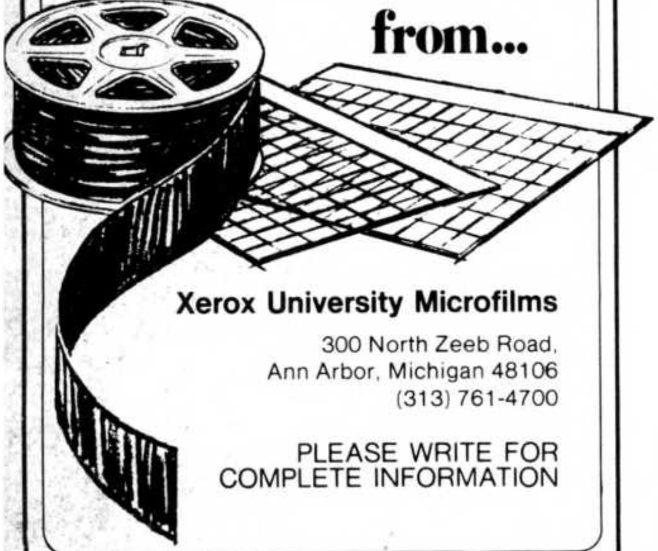

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Each 10 cc. ampul' or 5 cc. Concentrate vial'' provic

Ascorbic acid (C)	
Vitamin A*	10,000 U.S.
Vitamin D* (ergocalciferol)	1,000 U.S.
Thiamine HCl (B_1)	
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' With sorethytan laurate 1%, sodium hydroxide 1%; a
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1.6%; in Concentrate as riboflavin-5-phosphate.

* Oil-soluble vitamins A, D and E water solubiliz
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BRIEF SUMMARY

INDICATIONS: *in emergency feedings*—Surgery
sive burns, fractures and other trauma, severe in
diseases, comatose states, etc. may provoke a "str
uation with profound alterations in the body's m
demands and consequent tissue depletion of nutrien
result, wound healing may be impaired, enzyme act
turbed, hematopoietic tissues affected; hypoprot
and edema may appear; convalescence is thus prol
In such patients M.V.I. (administered in intraveno
under proper dilution) contributes optimum vitami
toward maintaining the body's normal resistance an
processes.

DIRECTIONS FOR USE: M.V.I. is ready for immed
when added to intravenous infusion fluids.
For intravenous feeding, one daily dose of 10 cc. of
5 cc. of M.V.I. Concentrate added directly to not le
500 cc., preferably 1,000 cc., of intravenous dextros
or similar infusion solutions...plasma, protein hydr
etc.

PRECAUTION: Allergic reaction has been known
following intravenous administration of solutions co
thiamine.

CAUTION: Not to be given as a direct undiluted intr
injection as it may give rise to dizziness, faintness, e

THERAPEUTIC NOTE: Intravenous use should be
tinued as early as practical in favor of an intramus
oral vitamin preparation, if deemed advisable.

HOW SUPPLIED: M.V.I.—10 cc. ampuls, boxes o
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in 100's only.

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USV PHARMACEUTICAL CORP.
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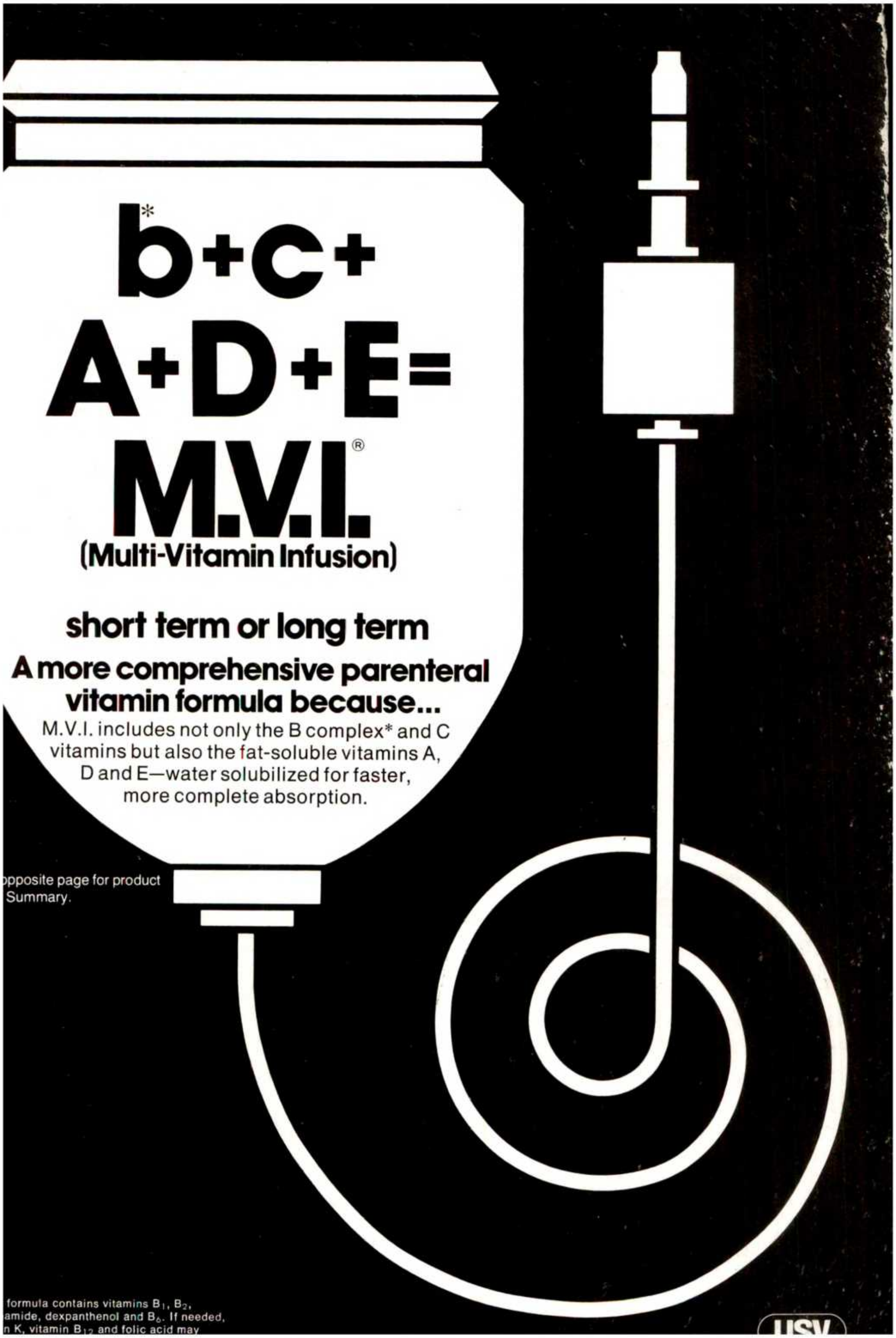

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M.V.I.®

(Multi-Vitamin Infusion)

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A more comprehensive parenteral vitamin formula because...

M.V.I. includes not only the B complex* and C vitamins but also the fat-soluble vitamins A, D and E—water solubilized for faster, more complete absorption.

pposite page for product
Summary.

formula contains vitamins B_1, B_2,
amide, dexpanthenol and B_6. If needed,
n K, vitamin B_{12} and folic acid may

USV

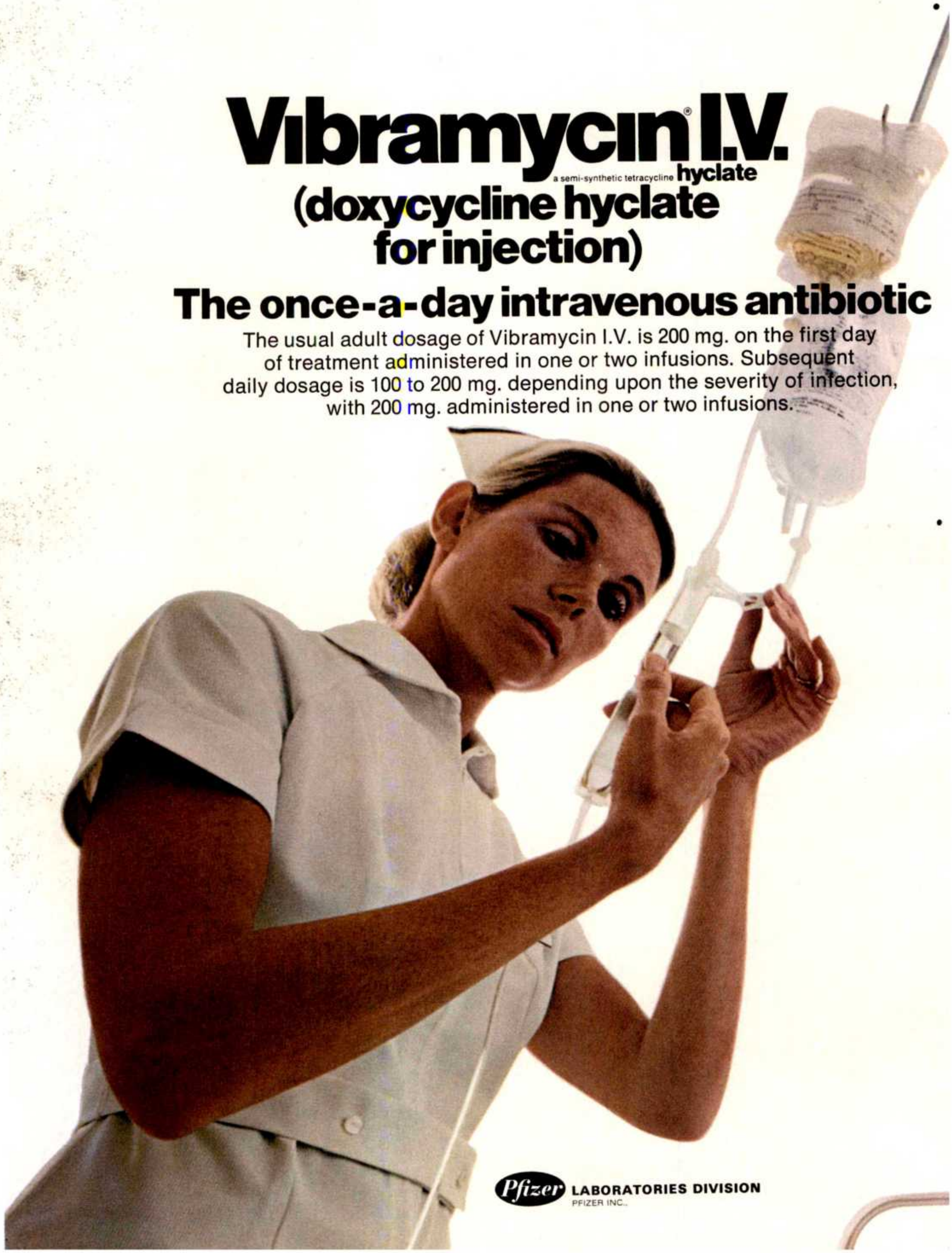
Vibramycin® I.V.

a semi-synthetic tetracycline **hyclate**

(doxycycline hyclate for injection)

The once-a-day intravenous antibiotic

The usual adult dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending upon the severity of infection, with 200 mg. administered in one or two infusions.



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1.

Effective in a wide range of surgical situations including bowel infections, peritonitis, pyelonephritis, cholecystitis, prostatitis, cellulitis, abscesses, and wounds

WHEN CAUSED BY SUSCEPTIBLE* STRAINS OF THESE ORGANISMS
Klebsiella pneumoniae,† *Enterobacter aerogenes, Escherichia coli,* Bacteroides

*Many strains of bacteria have been shown to be resistant to tetracyclines. These include strains of streptococci, pneumococci, and many gram-negative organisms. Therefore, culture and sensitivity testing are advisable to determine the susceptibility of the infecting organism to doxycycline.

†Respiratory and urinary infections.

2.

Studies to date have indicated that Vibramycin at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment

3.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage

See Brief Summary on following page for information on side effects, dosage and contraindications.

Vibramycin® I.V.

A semi-synthetic tetracycline **hyclate**

(doxycycline hyclate for injection)

Vials containing doxycycline hyclate equivalent
to 100 mg. doxycycline with 480 mg. ascorbic acid, and
200 mg. doxycycline with 960 mg. ascorbic acid

The once-a-day intravenous antibiotic

The usual adult dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending upon the severity of infection, with 200 mg. administered in one or two infusions.

Vibramycin® Hyclate (doxycycline hyclate) and
Vibramycin® Hyclate I.V. (doxycycline hyclate for injection)
BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. *Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.* Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a dark-field examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: *Note:* Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

More detailed professional information available on request.

For follow-up therapy / Vibramycin® hyclate Capsules

(doxycycline hyclate)
A semi-synthetic tetracycline

Capsules equivalent to
50 mg. and 100 mg. doxycycline

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How much has her rheumatoid arthritis improved?

Ring Size—measured in millimeters to evaluate swelling of finger joints

Walking time—determined by the number of seconds required to walk 50 feet

Grip strength—measured in millimeters of mercury using a rolled sphygmomanometer cuff

Inflammation index—arrived at by ascribing values of 1 to 4 to degree of pain, redness, swelling, tenderness, and presence of joint fluid; then totalling five parameters

Ascriptin® helps her get the most from aspirin therapy

When you specify Ascriptin, you're specifying Maalox®-protected aspirin. Ascriptin eases joint pain, stiffness and inflammation, while guarding against aspirin-induced gastric distress. That means your patient is more likely to tolerate the high dosage level of aspirin required to reduce arthritic inflammation. Thus, the patient will stay with an optimal dosage over an extended period, hopefully showing greater improvement. After all, if dosage is optimal, chances are that therapeutic benefits of Ascriptin will be, too.

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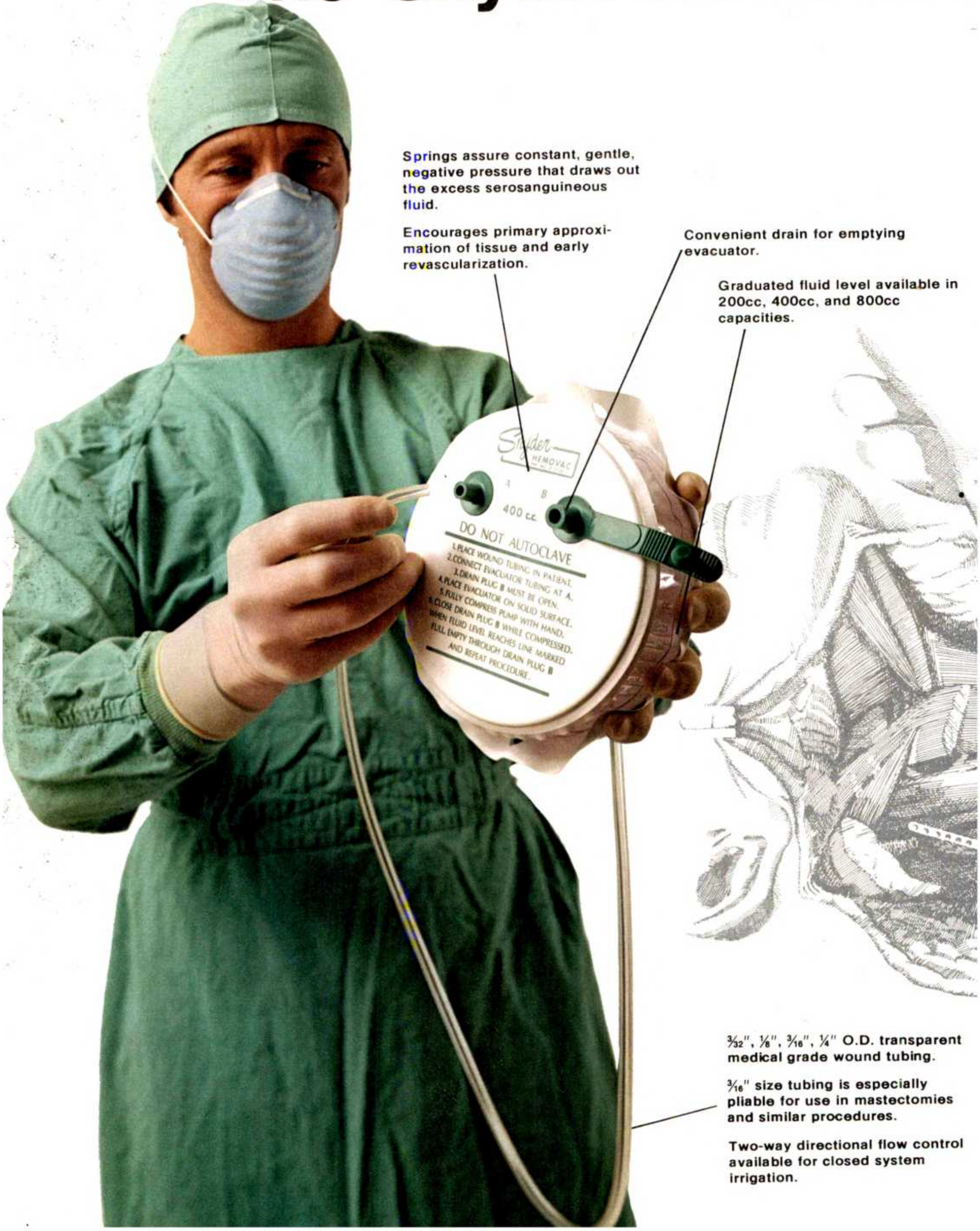
Snyder HEMOVAC
A
B
400 cc
DO NOT AUTOCLAVE
1. PLACE WOUND TUBING IN PATIENT.
2. CONNECT EVACUATOR TUBING AT A.
3. DRAIN PLUG B MUST BE OPEN.
4. PLACE EVACUATOR ON SOLID SURFACE.
5. FULLY COMPRESS PUMP WITH HAND.
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WHEN FLUID LEVEL REACHES LINE MARKED FULL, EMPTY THROUGH DRAIN PLUG B AND REPEAT PROCEDURE.

Springs assure constant, gentle, negative pressure that draws out the excess serosanguineous fluid.

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Convenient drain for emptying evacuator.

Graduated fluid level available in 200cc, 400cc, and 800cc capacities.

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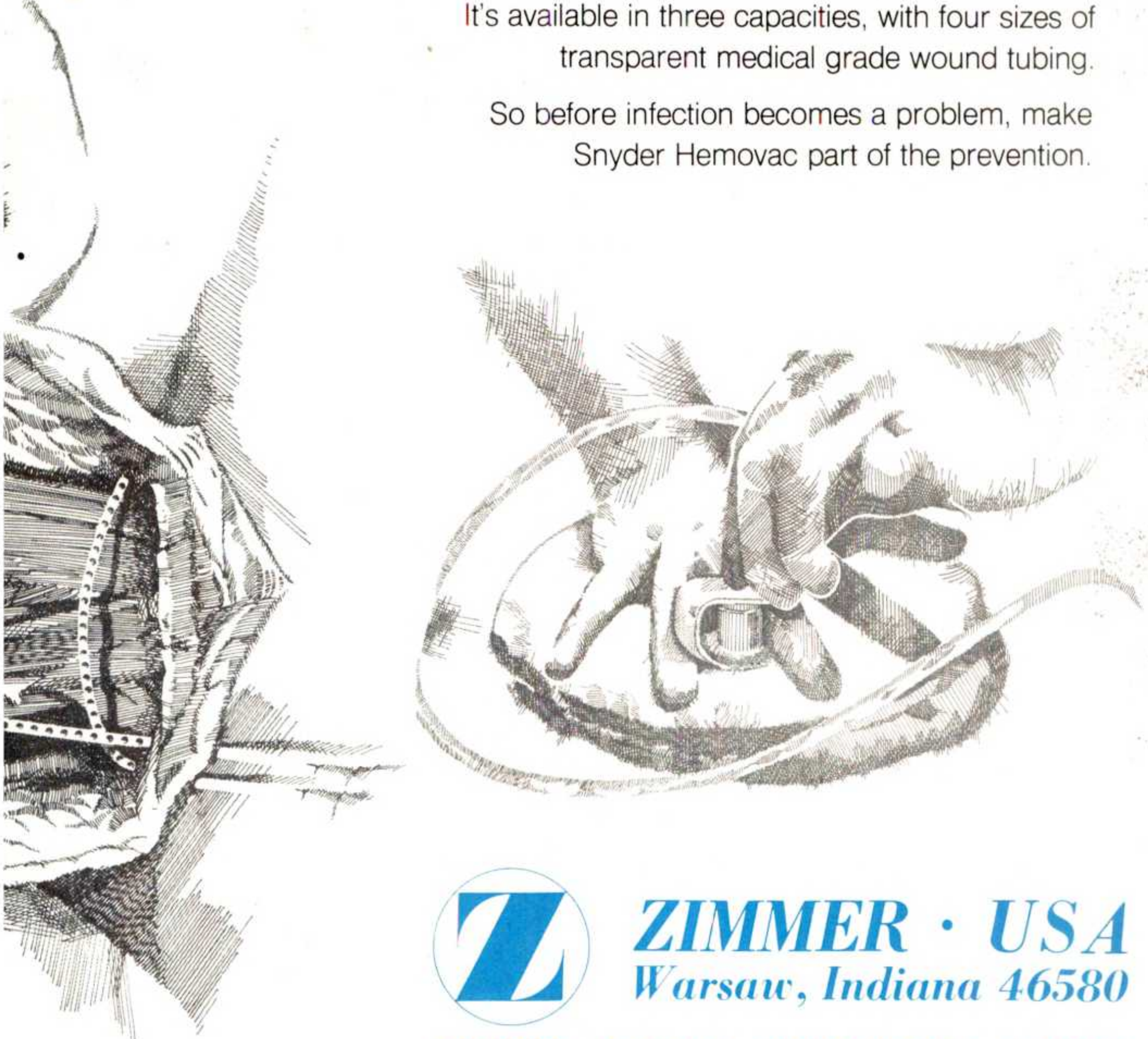
Constant, even suction aids infection control.

The Snyder Hemovac™ . . . the first practical, portable, disposable closed wound suction system. It's still first choice. It has proven so effective in reducing the incidence of post-operative infection that surgeons use it routinely.

The Snyder Hemovac has a wide range of alternatives. It's available in three capacities, with four sizes of transparent medical grade wound tubing.

So before infection becomes a problem, make Snyder Hemovac part of the prevention.



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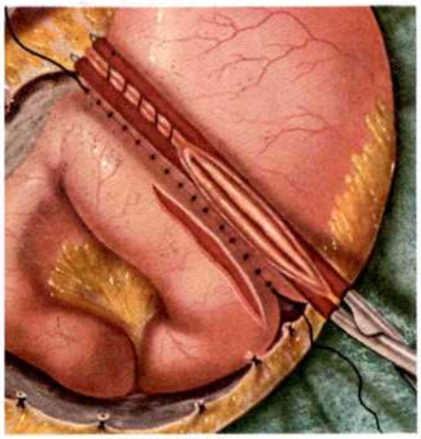
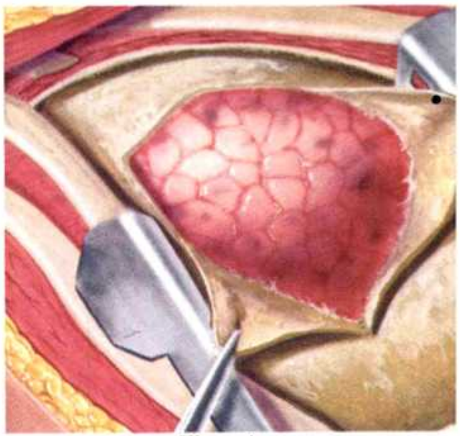
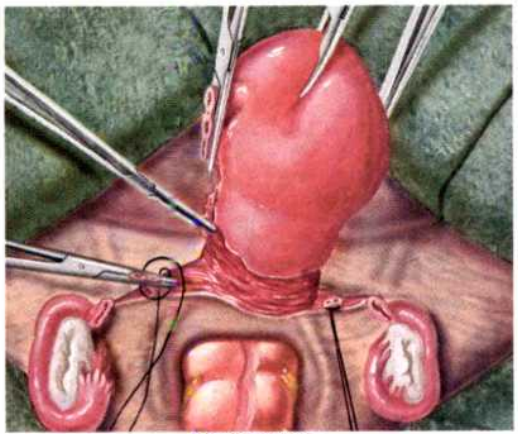
An unextreme parenteral analgesic can be preferable for the relief of moderate to severe pain associated with many everyday hospital situations.


Gastrectomy

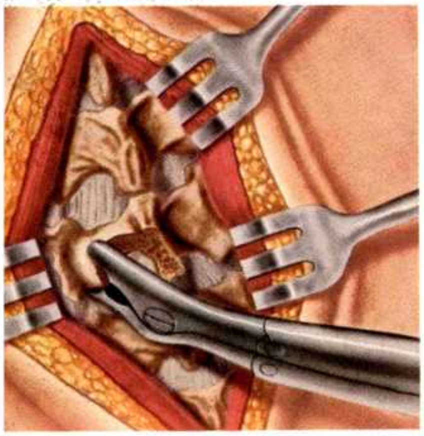
Ureteral colic


Thoracic surgery

Traumatic pain


Hysterectomy

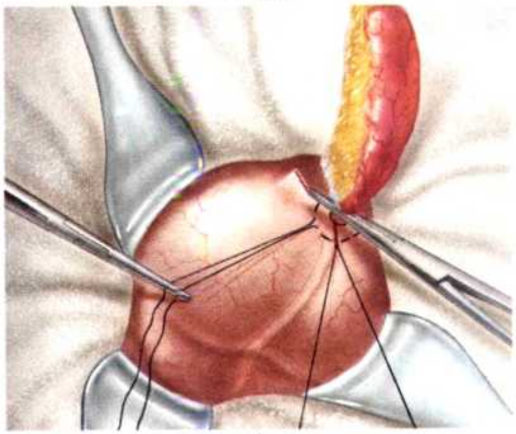
Endoscopy


Laminectomy

Burns

Multiple fractures

Acute bursitis


Appendectomy

Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

the unextreme injectable for serious pain

Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.

For most serious pain – Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy... with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.

In moderate to severe pain

Injectable **Talwin**®

brand of **pentazocine**

(as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp*T.M.*—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

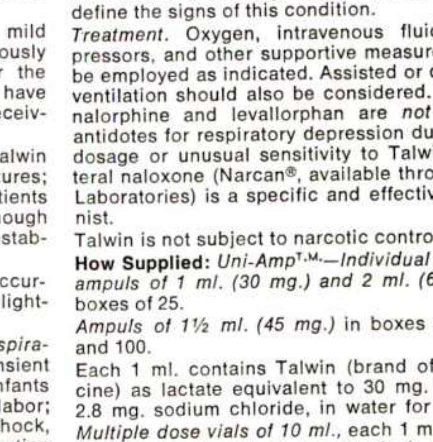
Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

(1639M)



the unextreme injectable for serious pain

Injectable
Talwin®
brand of
pentazocine
(as lactate)

Keflin® I.V.
sodium cephalothin
2 Gm.* in 100-ml. ampoule
*Equivalent to cephalothin.

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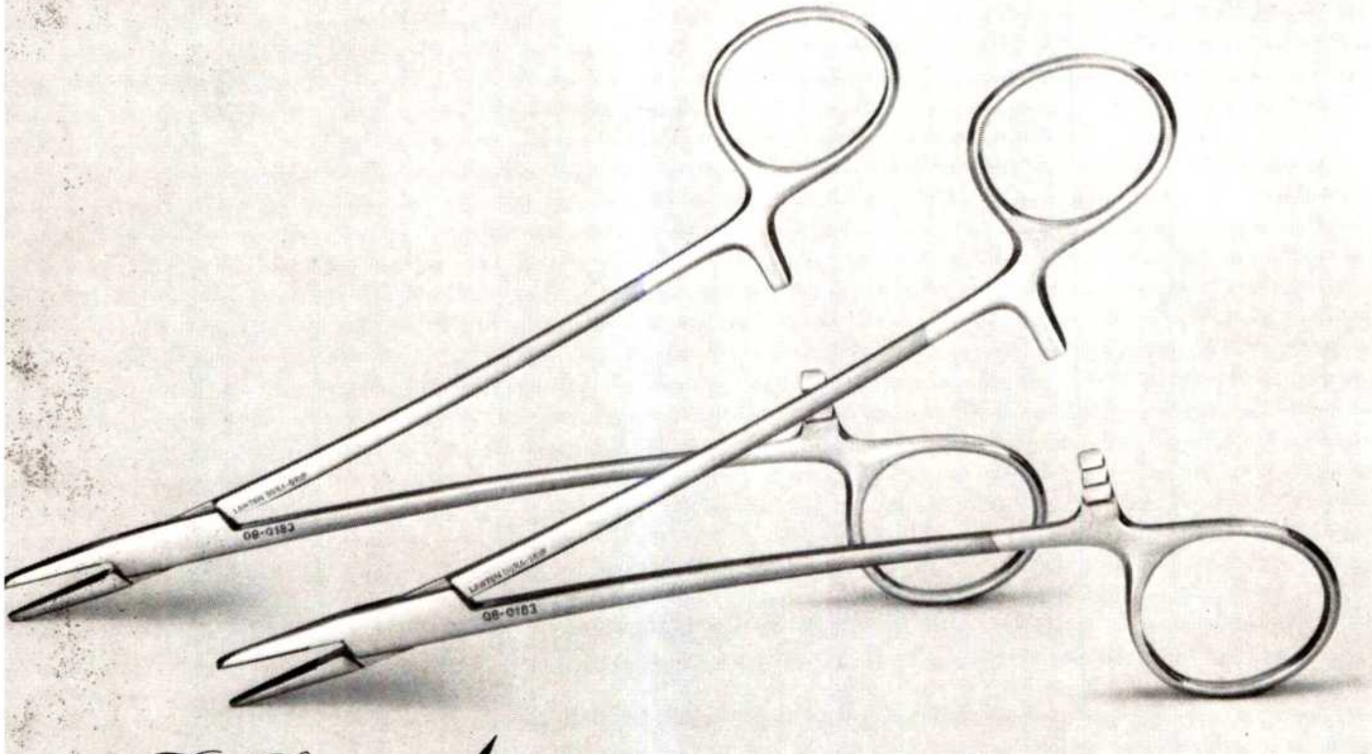
Only the Lawton Collection guarantees unvarying product uniformity in its entire line year after year.



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ATLAS OF SURGICAL TECHNIQUES

By Philip Thorek, M.D., F.A.C.S., F.I.C.S.

Illustrated by Carl T. Linden

From tracheostomy to subtotal gastrectomy, each procedure presented in this atlas has proven its advantages over and over again in the operating room. In collaboration with the brilliant medical artist Carl T. Linden, Dr. Thorek covers the surgical problems most frequently encountered in daily practice. You'll find pages devoted to procedures such as herniorrhaphy, splenectomy, thoracostomy, hemorrhoidectomy, etc. Each operative procedure is clearly presented, step-by-step, on a right hand page, with explanatory text on the facing page.

Where competitive techniques for given conditions exist, Dr. Thorek states his preferences with characteristic clarity and candor. Every choice is critically discussed and firmly supported in the detailed presentations.

All the illustrations are original, the text type is large and legible, and the beautiful illustrations are labelled with maximum clarity. The author's reputation as a medical communicator is once again demonstrated in this, his latest work.

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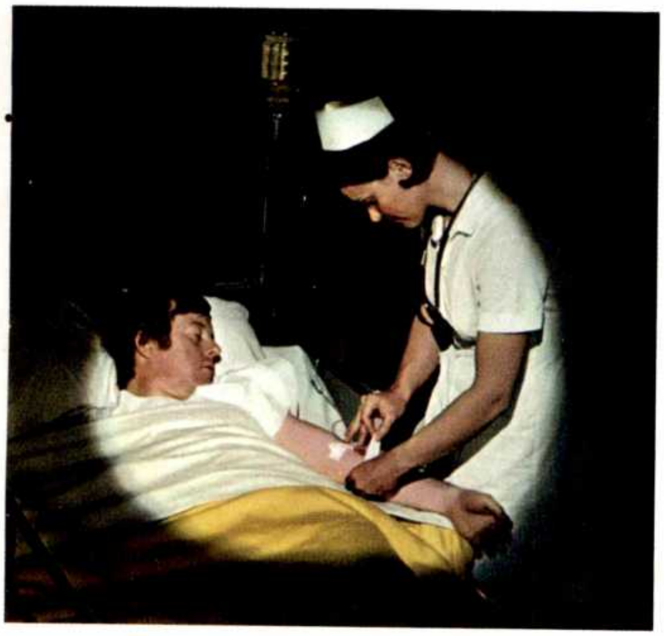
Effective performance in postsurgical and other serious susceptible hospital infections

Bacteriologically controlled studies demonstrated efficacy in patients with:

- Skin and soft-tissue infections due to *Staphylococcus aureus*, including penicillin G-resistant staph, Group A beta-hemolytic streptococci or *E. coli.*
- Respiratory tract infections due to *D. pneumoniae*, Group A beta-hemolytic streptococci, Klebsiella spp. or *H. influenzae*.
- Genitourinary tract infections due to *E. coli*, *P. mirabilis*, Klebsiella spp. or *Staphylococcus aureus*, including penicillin G-resistant staph.



Low incidence of venous irritation on I.V. administration... well tolerated locally

In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low. *Controlled studies* in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly.

Cephalosporins are reported to produce maculopapular rash, urticaria, reactions resembling serum-sickness and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

In penicillin-allergic patients, cephalosporins should be used with great caution. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins, and there are instances of patients who have had reactions to both drugs (including fatal anaphylaxis after parenteral use).

Flexible Dosage: adjustable to fit severity of infection and renal status of patient:

The usual adult dose of Cefadyl is 0.5 Gm. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. Doses up to 12 Gm. daily may be used in very serious or life-threatening infections.

No nephrotoxicity reported during extensive clinical trials

In fact, when Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported. However, renal status of patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate. Rises in BUN have been observed; their frequency increases in patients over 50 years old. (See Dosage, Adults—in Prescribing Information on last page.)

Cefadyl® IV/IM
sterile cephapirin sodium

Please see next page for Prescribing Information.

BRISTOL

Cefadyl® IV/IM
sterile
cephapirin sodium

Effective performance in surgical and other serious susceptible hospital infections

CEFADYL® (sterile cephapirin sodium) 7628 DIRO-07 July 1974

Description. Cefadyl (sterile cephapirin sodium) is a cephalosporin antibiotic intended for intramuscular and intravenous administration only. It is supplied as the sodium salt of 7-[α-(4-pyridylthio)-acetamido]-cephalosporanic acid. Each 500 mg. contains 1.18 milliequivalents of sodium.

Actions. *Human Pharmacology*—Following intramuscular administration of single 500-mg. and 1-Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

Cefadyl and its metabolites were excreted primarily by the kidneys. Antibiotic activity in the urine was equivalent to 35% of a 500-mg. dose 6 hours after I.M. injection, and to 65% of a 500-mg. dose 12 hours after injection. Following an I.M. dose of 500 mg., peak urine levels averaged 900 mcg./ml. within the first 6 hours.

Following rapid intravenous administration of single 0.5-Gm., 1-Gm., and 2-Gm. doses, peak serum levels of 35, 67, and 129 mcg./ml. respectively, were attained at 5 minutes, declining to 6.7, 14.0, and 31.7 mcg./ml. respectively, at 30 minutes and 0.27, 0.61, and 1.11 mcg./ml. respectively, at 3 hours.

Seventy percent of the administered dose was recovered in the urine within 6 hours. Repetitive intravenous administration of 1-Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—*In vitro* tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro:*

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis*, are relatively resistant.)

Staphylococci, including coagulase-positive, coagulase-negative, penicillinase, and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli,* Klebsiella species.

Most strains of enterobacter and indole-positive Proteus (*P. vulgaris, P. morganii, P. rettgeri*) are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima, and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections, and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organism and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution, or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. The lower dose of 500 mg. is adequate for certain infections, such as skin and soft tissue and most urinary tract infections. However, the higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Grams daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patients with reduced renal function (moderately severe oliguria or serum creatinine above 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./Kg. of cephapirin every 12 hours. Patients with severely reduced renal function and who are to be dialyzed should receive the same dose just prior to dialysis and every 12 hours thereafter.

Children—The dosage is in accordance with age, weight, and severity of infection. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb.) administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treatment of children under the age of three months the relative benefit/risk should be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at least 10 days.

Where indicated, surgical procedures should be performed in conjunction with antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intravenous routes.

Intramuscular Injection—The 1-Gm. vial should be reconstituted with 2 ml. of Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin. All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients with bacteremia, septicemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. If patient has impaired renal function, a reduced dose may be indicated (see *Dosage, Adults*). In conditions such as septicemia, 6 to 8 Gm. per day may be given intravenously for several days at the beginning of therapy; then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment and multiple sites have been involved, daily doses up to 12 Gm. have been used.

For patients who are to receive cephapirin intravenously it is convenient to use the 1-Gm., 2-Gm., or the 4-Gm. vial (See Precautions).

Intermittent Intravenous Injection—The contents of the 1-Gm. vial should be diluted with 10 ml. or more of diluent and administered slowly over a 3- to 5-minute period or may be given with intravenous infusions.

The 2-Gm. vial should be diluted with Dextrose Injection, U.S.P. or Sodium Chloride Injection, U.S.P. When only 20 to 25 ml. are added, Sterile Water for Injection, U.S.P. may be used. The table below gives concentrations for various diluent volumes.

Diluent Added (ml.)	*Solution Concentration*	*Grams per ml.*
100	1 Gm. per 50 ml.	0.020
50	1 Gm. per 25 ml.	0.040
20	1 Gm. per 10 ml.	0.100

Intermittent Intravenous Infusion with Y-Tube—Intermittent intravenous infusion with a Y-type administration set can also be accomplished while bulk intravenous solutions are being infused. However, during infusion of the solution containing Cefadyl (sterile cephapirin sodium), it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to the volume of the solution containing Cefadyl so that the calculated dose will be infused. When a Y-tube hookup is used, the contents of the 4-Gm. vial of cephapirin should be diluted by addition of 40 ml. of Sterile Water for Injection, U.S.P., 5 percent Dextrose Injection, U.S.P., or Sodium Chloride Injection, U.S.P.

Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added to the solutions listed below under *Stability*. The choice of solution and volume should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability:* After reconstitution, it is stable for 12 hours at room temperature or 10 days under refrigeration when reconstituted with Sterile Water for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5 During these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

Compatibility with the Infusion Solutions: Cefadyl is stable and compatible for 24 hours at room temperature at concentrations between 2 mg./ml. and 30 mg./ml. in the following solutions:

Sodium Chloride Injection, U.S.P., 5% W/V Dextrose in Water, U.S.P., Sodium Lactate Injection, U.S.P., 5% Dextrose in Normal Saline, U.S.P., 10% Invert Sugar in Normal Saline, 10% Invert Sugar in Water, 5% Dextrose + 0.2% Sodium Chloride Injection, U.S.P., Lactated Ringer's with 5% Dextrose, 5% Dextrose + 0.45% Sodium Chloride Injection, U.S.P., Ringer's Injection, U.S.P., Lactated Ringer's Injection, U.S.P., 10% Dextrose Injection, U.S.P.

Supply. Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapirin sodium equivalent to 1 Gm., 2 Gm., or 4 Gm. cephapirin. NDC 0015-7628—1-Gm. vial. NDC 0015-7629—2-Gm. vial. NDC 0015-7630—4-Gm. vial.

For information on package sizes available, refer to the current price schedule.

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*Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

Diabetes Insipidus Secondary to Penetrating Thoracic Trauma

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Three cases of diabetes insipidus following non-cranial trauma are presented. They are believed to be the first of their kind reported. The etiology, pathogenesis and differential diagnosis of diabetes insipidus are discussed. The literature if briefly reviewed and similarities between patients with DI due to long bone trauma with fat embolism, post open heart surgery hypotension, Sheehan's syndrome following postpartum hemorrhage, DI and our own patients are discussed. It is concluded that the diabetes insipidus is caused by selective disruption of posterior pituitary circulation due to fat globules, thrombi and hypovolemia resulting in hypoxia and tissue necrosis.

DIABETES Insipidus is an uncommon disease entity characterized by polyuria and polydysia. It arises from one of several causes and can be classified as either primary or secondary.[3] The primary causes are either idiopathic or familial. The secondary group consists mainly of pituitary tumors usually a chromaphobe adenoma, or other neoplasm near the pituitary or hypothalamic regions. In addition, secondary diabetes insipidus can result from granulomata involving the pituitary and trauma to that area. The latter usually consists of direct head injury with disruption of the hypothalmic-posterior pituitary axis. Recently we have seen three patients with post traumatic diabetes insipidus secondary to penetrating chest trauma unassociated with head injury. A thorough search of the English literature revealed only four documented patients with diabetes insipidus which even remotely resemble the three cases presented herein.[2,6,7]

Case Reports

Case 1. A 17-year-old black male was admitted to the Martland Hospital on October 22, 1972 with a stab wound in the precordial area. The vital signs were absent and the pupils were dilated. He was intubated, ventilated and the fluid volume replaced with crystalloid solution and later type specific cross matched blood. He was immediately taken to the operating room where a 2 cm laceration at the apex of the right ventricle was closed. Following this, restoration of cardiac action was obtained and the blood pressure restored to normal. Postoperatively he had spontaneous respirations and his previously fixed, dilated pupils were smaller and reacted to light. However he remained comatose and generalized convulsions supervened. These were controlled with diphenylhydantoin, phenobarbital, curare, and moderate external hypothermia. Five mgm of dexamethasone sodium phosphate were given every four hours to reduce cerebral edema. On the sixth postoperative day, he began excreting large amounts of diluted urine with a specific gravity of 1.005 without abnormal substances such as glucose or protein. A tentative diagnosis of diabetes insipidus was made which was further substantiated by administration of 10 units of intramuscular aqueous pitressin. This reduced his hourly urine output from in excess of 400 ml/hour to less than 100 ml/hour. He was maintained on pitressin until he expired five days after the onset of diabetes insipidus. During this time his rectal temperature ranged 33–37 C.

Postmortem examination disclosed coagulation necrosis of the anterior pituitary with mild acute inflammatory infiltration. A large thrombus was noted in the vein surrounding the pituitary capsule with the capsular tissue also showing acute inflammatory changes (Fig. 1). The posterior pituitary presented hemorrhage and acute and chronic inflammatory infiltrates (Fig. 2). There was widespread necrosis of neurons which was more marked in the cortex than in the pons. The outer zones of the cortex showed acute inflammatory infiltrates which were mainly perivascular. Fibrin thrombi were noted in the meningeal vessels. The right kidney was congested and multiple small fibrin thrombi were noted in the outer cortex that were not related to glomeruli. Acute tubular necrosis was not observed.

Case 2. J.C., a 15-year-old black male was admitted to the Martland Hospital August 23, 1972 in severe respiratory distress from a gunshot wound of the right chest. Following intraveneous Ringer's Lactate his arterial blood pressure rose from 60/0 to 100/20. Because of marked neck vein distention and drainage of only 15 cc of blood following an insertion of a chest tube, he was immediately taken to the operating room where a right thoracotomy revealed cardiac tamponade, a 2 cm hole in the right atrium and a laceration of the right lung. These were repaired and the patient sent to the surgical intensive care unit with an arterial blood pressure of 110/70.

However, he was non responsive and the pupils were fixed and dilated. The next 12 hours his urinary excretion averaged 425 ml/hour, at one point increasing to 1100 ml/hour for two hours. A tentative diagnosis of post-traumatic diabetes insipidus was made and 10 units of aqueous pitressin were given intramuscular. This reduced the urine output to about 150 cc/hour for the next five or six hours. His BUN at this time was 12 mgm% and the serum sodium was 146 mEq/L. The urine output again began to rise and the following day it was averaging 310 ml/hour. His serum osmolality was 336 mOsm/L and the urine osmolality was 64 mOsm/L. Specific gravity of the urine was 1.001 and there was no glucose or acetone

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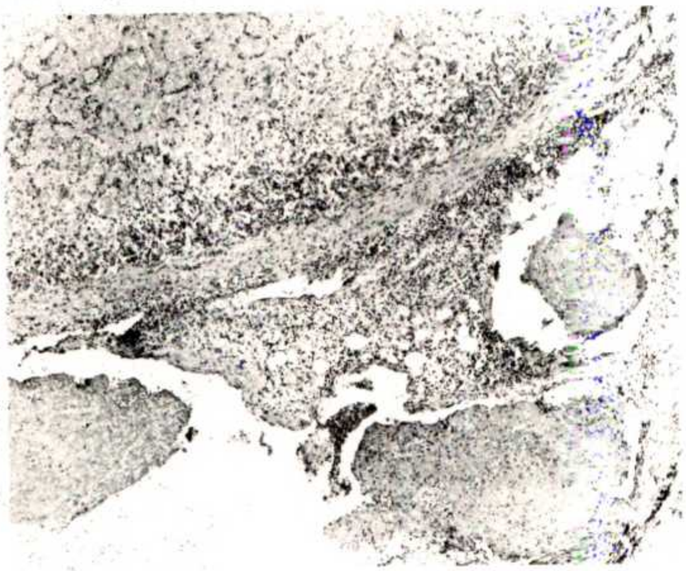

FIG. 1. Section of pituitary capsule demonstrating a large thrombus in vein. There is also noted an acute in flammatory infiltrate in the capsular tissues.

present. Following another injection of 10 units of pitressin the urine out put averaged 50 ml/hour, serum osmolality was 357 and the urine osmolality was 212. The following day without additional pitressin the serum osmolality was 361, the urine osmolality 402 with a urine output averaging 50 ml/hour. His rectal temperature ranged 33–37.5 C until he expired on the fourth postoperative day. Unfortunately the pituitary was not obtained at postmortem. However, sections taken from the cerebral cortex revealed no histologic changes. The kidneys did not show acute tubular necrosis.

Case 3. An 18-year-old female entered the Martland Hospital Emergency Room on January 9, 1973 with a stab wound of the left infraclavicular region at the outer third of the clavicle. The blood pressure and pulse were unobtainable and the patient was agonal with dilated but reactive pupils. Resuscitative measures included intubation, rapid infusion of 6 L of Ringer's Lactate followed by 6 units of blood. An immediate left anterior thoracotomy was performed in the emergency room with cardiac massage and ligation of the transected axillary artery. The vital signs returned and the patient was taken to the operating room where the partially transected axillary vein was repaired along with a laceration of the left lung, and the axillary artery. Postoperatively the blood pressure was 120/60, the pulse was 120, the CVP cm H_2O and the urine output was 90 cc/hour. The patient remained unconscious but stable. On the fifth postoperative day the patient has a respiratory arrest but was immediately resuscitated. Following this the urine output increased to an average of 550 ml/hour, and the diagnosis of diabetes insipidus was made. The serum osmolality was 329 with a urine osmolality of 92. Pitressin was given which increased the urine osmolality to 363. The urine output then averaged 250 ml/hour. On the sixth post-operative day the patient had a second cardiac arrest and expired. Postmortem examination of the anterior pituitary revealed coagulation necrosis with multiple foci of hemorrhage (Fig. 3). Recent thrombi were noted in the parietal venous vessels. The posterior pituitary showed small focal hemorrhage and edema. The cerebral cortex had focal hemorrhagic infarcts with subcortical white matter hemorrhage. Anoxic neuronal changes were noted in the substantia nigra but these were not associated with hemorrhage. The kidneys were congested but there was no evidence of acute tubular necrosis.

Discussion

Regardless of its etiology the primary pathogenetic factor in true diabetes insipidus is a lack of circulating antidiuretic hormone (ADH). This hormone is an octapeptide manufactured in the superoptic nuclei and paraventricular of the hypothalamus and transported along the hypothalamic posterior pituitary axis to be stored in the gland. It is normally released from the gland upon one or both of two stimuli. The first is a variation in the extracellular fluid volume (ECF). As the ECT is decreased, there is a concomitant increase of ADH released. This mediated through volume receptors located in the left atrium of the heart and in the aortic arch or carotid artery. The second stimulus to release of ADH is an increase of plasma osmolality mediated through osmoreceptors in the internal carotid artery. After ADH is released from the posterior pituitary, it exerts its action directly on the kidney. The cite of action in the kidney is believed to be primary in the distal loop of Henle, the distal convoluted tubule and the collectint duct system. The hormone acts by making the cells of the distal nephron in the collecting duct more permeable to the passage of water, thereby allowing the normal hypertonic interstitium of the renal medulla to exert its osmotic effect on the hypotonic content of the tubles, that is, the urine. This draws water from the urine and makes it hypertonic in relation to the plasma allowing metabolities to be excreted without dehydrating the patient. The exact mechanism by which ADH exerts its effect on tubular cells is not well delineated although currently it is believed that like many other hormonal systems it is mediated by cyclic 3′ to 5′ AMP.

Panhypopituitarism was first described by Simmons in 1914.[12] He believed that the disease was caused by septic emboli resulting in infarct necrosis of the adenohypophysis. In 1938 Sheehan and Murdock[10] described a syndrome of postpartum pituitary necrosis in patients who were in shock

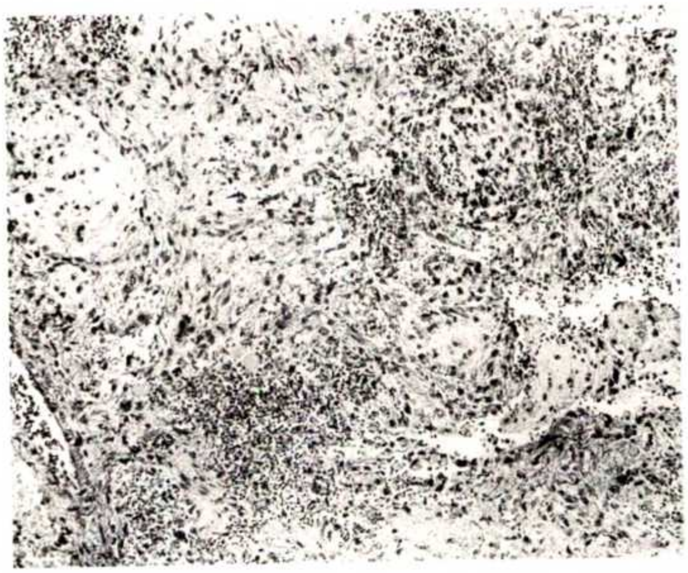

FIG. 2. Section of posterior pituitary showing hemorrhage, and acute and chronic inflammatory infiltrate.

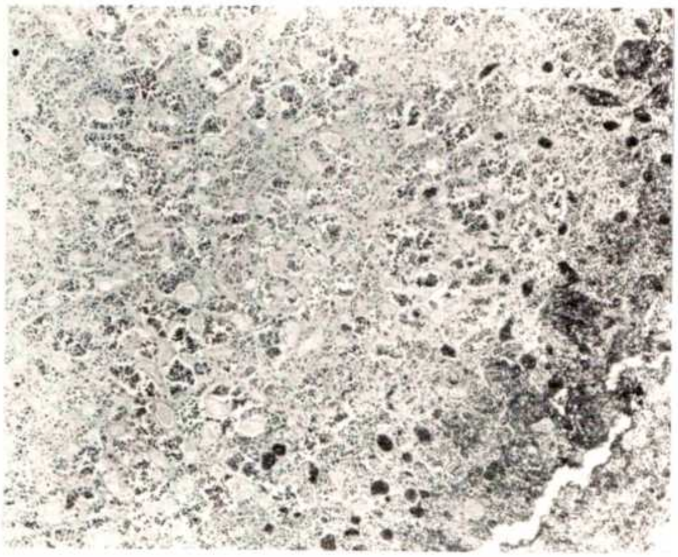

FIG. 3. Section of posterior pituitary showing hemorrhage, and acute and chronic inflammatory infiltrate.

from hemorrhage after parturition. They noted that the circulation to the anterior pituitary was decreased at normal delivery and postulated if a circulatory collapse were to occur the diminished blood flow would result in vascular thrombosis in the gland. In 1961 Sheehan and Stanfield[11] claimed that the primary vascular disturbance during severe hemorrhage was arterial spasm with subsequent vascular thrombosis. They believed that the degree and severity of anterior pituitary necrosis was related to the duration and severity of the occlusive process. Later Sheehand and Whitehead[9] even extended this theory to encompass posterior necrosis in order to explain the occurrence of diabetes insipidus.

Another hypothesis to explain the pathophysiology of the pituitary insufficiency during pregnancy was advanced in 1962 by Beernink and McKay.[1] They showed that thrombosis, hemorrhage and necrosis of the hypothalamus, pituitary stalk and both lobes of the pituitary occurred in the presence of disseminated intravascular coagulation (DIC). Since ADH or its precursor is formed in the supraoptic and paraventricular nuclei in the hypothalamus and is carried along the tracks of the pituitary stalk to be stored in the posterior lobe of the pituitary, damage to any of these areas can result in diabetes insipidus. When secondary to trauma diabetes insipidus is usually due to closed head inuries in which the hypothalamic posterior pituitary ransport mechanism is affected when the stalk is disrupted by shearing forces. The blood supply to the posterior pituitary usually remains intact since it is derived directly rom the inferior hypophyseal artery. However, the neuronal paths along the neurosecretory granules travel are nterrupted, thereby cutting off flow of the hormone to the pituitary making its release impossible.

Since there was no evidence of a head injury in our patients, it is possible that the polyuria could have been due to iatrogenic fluid overloading. However, in this instance, hyponatremia and a low serum osmolality should be evident. By contrast the patient with diabetes insipidus is dehydrated from his polyuria and has a high serum osmolality. Positive proof for polyuria resulting from overhydration could have been the use of the water deprivation test. In this test, fluid is withheld until an individual has lost 3% of his body weight. With this amount of fluid loss, the ECF is reduced enough to cause maximal ADH secretion. When the primary problem is overexpansion of the extracellular fluid, the urine output should decrease to 0.5 mg/minute, the urine specific gravity rise to 1.020 or more and the urine osmolality approach 800 mOsm. In the absence of nephrogenic diabetes insipidus, when the above changes in the urine are not observed, it may be assumed that an absolute deficiency of ADH exists. We did not employ this test in our patients because of the obvious danger in subjecting someone to a loss of 3% body weight following major trauma and surgery. Instead we relied upon serum and urine osmolality serum sodium and plasma protein values plus the clinical state of the patient as a guide to the state of hydration.

The second most common cause of polyuria in the recently traumatized patient, is acute renal failure, with tubular necrosis, in which the patient goes directly into the diuretic phase without over being oliguric. In this condition there is usually a rising BUN and serum creatine associated with a urine that contains tubular casts and is isotonic with plasma. None of the above mentioned were present in our patients nor was acute tubular necrosis seen on the autopsy specimens.

Other less common causes are nephrogenic diabetes insipidus and diabetes mellitus. The former would manifest itself identically with true ADH deficient diabetes insipidus but would not respond to ADH infusion. The latter can be ruled out by the lack of glucose in the urine and a hypotonic rather than a hypertonic urine. The blood sugar in all our patients were normal.

The definitive diagnostic test for DI is the response to exogenous ADH. Intramuscular injection of 10 units of aqueous vasopressin should result in marked diminution in urine volume and a significant increase in the osmolality of the urine. This is precisely what happened in our patients. In Case 1 osmolality studies were not obtained but immediately following injection of ADH the urine flow decreased from 400 ml/hour to less than 100 ml/hour. In the second case, where vasopressin was given the preinjection urine osmolality was 64 mOsm/L and the volume was 310 ml/hour. Following the injection of vasopressing the flow decreased less than 50 ml/hour and the osmolality immediately increased to 212 mOsm/L and eventually to 402 mOsm/L. Similarly in the third patient following the injection of pitressin the urine osmolality increased from 92 to 363 mOsm/L and the urine output declined from an average of 550 ml/hour to 250 ml/hour.

A comprehensive review of the literature has revealed only three cases of diabetes insipidus in traumatized patients who had not received closed head injuries. Hanson[2] reported two patients and Rottenberg[7] another individual, who developed diabetes insipidus from systemic fat emboli, secondary to long bone features. The mechanism responsible for the pituitary dysfunction was thought to be actual disruption of the circulation to the posterior lobe by fat emboli since fat globules were seen in the pituitary vessels in one of Hanson's patients who was autopsied.

The syndrome of DI following trauma in which the head is not involved is probably a secondary manifestation of shock. Robinson and Pagliero[6] reported the development of DI in a 15-year-old girl following open heart surgery. She was in shock secondary to cardiac tamponade and developed polyuria on the fifth postoperative day. With the use of exogenous pitressin she recovered with no sequalae. Similar recovery has been observed in patients with panhypopituitarism after postpartum hemorrhagic shock.

In all probability, the pathogenesis in our patients was due to inadequate tissue perfusion. Fibrin and whole blood thrombi are both commonly seen in the shock state. The former was noted in case 1 in several areas. However, this was not associated with the clinical picture of DIC as with Beernink's patients. Thrombi can also occur as a terminal event. The whole blood thrombi located in the capsule of the pituitary in case 1 and in the parietal vessels in case 3 are similar to those seen in the cases reported by Sheehan. Since cases 1 and 3 revealed anoxic changes of the cerebral cortex, the mechanism that best explains the syndrome in our patients is shock from hypovolemia with occlusion of vessels resulting in tissue hypoxia and necrosis.

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The Effect of Differing Ambient Oxygen Tensions on Wound Infection

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Wound infections were studied in rabbits using two standard inocula ($\simeq 10^4$ and $\simeq 10^6$) of *Pseudomonas aeruginosa* injected into a subcutaneous wound dead space made by implantation of standard wire mesh cylinders. The inoculation was done on the fourth day after implantation of the cylinders in animals kept from the day of implantation in atmospheres of 12%, 21%, or 45% oxygen content. Samples of wound fluid (0.2 ml) were removed for quantitative culture just before inoculation and 3, 7, 14, and 21 days later. No positive cultures resulted from samples taken before inoculation. One uninoculated wound served as a control in each animal. None of these control wounds became infected. Culture counts were significantly highest in the anoxic group and lowest in the hyperoxic group. Established infections were significantly lowest in the hyperoxics and highest in the hypoxics. The percent of wounds showing a significant culture count showed a similar trend. The mechanisms of this effect is not known, but a possible mechanism lies in the relative inability of leucocytes to kill this bacterium under hypoxic conditions.

WOUNDS IN TISSUES with a poor blood supply become infected far more frequently than wounds in tissue that have good perfusion. Severely traumatized and hypoxic patients seem to be unusually susceptible to infection. Experimentally, impairment of tissue perfusion by vasoconstrictors or hemorrhagic shock enhances infections at sites in which bacteria are injected.[2] Tissue trauma at a distance from the wound impairs healing, decreases the already tenuous oxygen supply to the wound, and increases susceptibility to infection,[2,4] but this increased susceptibility to infection can be reduced by restoring the blood-oxygen supply to the wound.[4]

Obviously, there is a good circumstantial argument for associating tissue hypoxia with infectability. However, as far as we are aware, the relationship of infectability of soft-tissue wounds to chronic hypoxia and hyperoxia at atmospheric pressures has never been studied.

In previous studies from this laboratory the composition of extracellular fluid in wounds of animals exposed to hypoxic, normoxic, and hyperoxic environments was investigated.[8,9] Varying ambient oxygen concentrations profoundly affected wound metabolism and the rate of collagen synthesis. The present study was designed to test susceptibility to wound infection in animals that chronically breathed fixed concentrations of 14%, 20% and 45% oxygen.

Methods

Three or four stainless steel, wire mesh cylinders 5 cm long and 6.5 cm in circumference were implanted under sterile conditions beneath the dorsal skin of 35 anesthetized New Zealand White rabbits by methods previously described.[9] After the skin was closed over the cylinders and the animals awakened from anesthesia, they were placed into lucite boxes approximately 70 L in volume, into which a gaseous mixture was pumped at approximately 3 L per minute per rabbit. By adjusting the inflow rate, the ambient pCO_2 was kept below 0.5%. Temperature remained 24–28 C, and humidity 70–90%.

Three ambient atmospheres were used; hyperoxic, 42% to 46% oxygen, normoxic, 21% (air), and hypoxic, 12% to 14% oxygen. The hyperoxic mixture was obtained by passing pure oxygen through a Venturi type gas mixer and diluting it with air (Puritan,® 40% setting). The 5% increment above the rated value of the instrument was due to a slight resistance in our gas conducting tubes. The normoxic and hypoxic mixtures were obtained by passing air or nitrogen through an identical mixer on the same setting. This method gives reliable gas mixtures over long periods at minimal expense.

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On the fourth day after implantation of the cylinders, when the tissues had adhered to the wire mesh, a 0.2 ml sample of wound fluid was aspirated aseptically from each wound cylinder and was cultured. All specimens yielded no growth. Selected wound cylinders were then injected with a known number of Pseudomonas aeruginosa prepared as follows:

An overnight culture of an established strain of *Pseudomonas aeruginosa* was diluted to 10^2 and 10^4 dilutions. Each dilution was sampled for bacterial count by the culture plate technique, and 0.2 ml of the resuspended culture was inoculated into the selected wounds. One wound was inoculated with sterile broth (control), two wounds were inoculated with a small bacterial inoculum (1.6×10^4 to 3.3×10^5) and one wound was inoculated with a large bacterial inoculum (1.3×10^6 to 7.7×10^6). In the few cases in which only 3 wounds were made, one was a control, one received the lower and one the higher inoculum.

On days 3, 7, 14, and 21 after inoculation, the skin over the dorsal end of each wound was shaved and treated with tincture of iodine. Two tenths ml of fluid was aspirated from each wound cylinder and was immediately placed into nutrient broth. The bacteria in these specimens were promptly counted by the culture plate technique. The specimens were coded, and the cultures and counts were done by one of us (M.S.) who was unaware of the source of the specimen. Statistical comparisons of all results were done by Fischer's exact test.

Another group of 12 animals was kept in the experimental atmospheres, 4 animals in each atmosphere. The arterial and wound gases were measured by standard techniques on the fourth post-implantation day.

Results

Figures 1 and 2 show the mean bacteria counts found in wounds on selected days. In general, the higher counts occurred in hypoxic animals and the lower counts in the hyperoxic group.

Bacteria counts of 5×10^2 or greater were arbitrarily considered as "infections." Significant differences in the numbers of "infected" wounds between the air and 45% oxygen breathing rabbits ($p < 0.05$) were found on days 3, 7, and 14 in the wounds inoculated with the large inoculum. The difference between the numbers of wounds "infected" in the hypoxic and air groups was smaller and not significant. The differences between the hypoxic and hyperoxic groups were statistically significant ($p < 0.05$) on all test days.

In the low inoculum groups, statistically significant differences in the number of wounds "infected" were obtained between the air and hyperoxic groups only at 7 days. Once again the differences between hypoxia and hyperoxia breathing were greater with p values of less than 0.06 at 7 and 21 days. The small overall "infection" rates account fo the small differences found.

The distribution of bacteria counts differed also betwee the groups. Figure 3 shows the range of bacteria counts fo the high inoculum groups at day 7. In general, the hyper oxic group had the lowest count, the normoxic group was in termediate, and the hypoxic group had the highest counts When these and other such data for the other days wer plotted on a 2 × 2 matrix using Fischer's exact test, number of differences were found with p values of less tha 0.01 between normoxic and hypoxic groups as well a between hyperoxic and normoxic groups.

As we and others have previously shown, occasiona cultures, even in wounds which appeared grossly infected were negative. For purposes of analysis, then, a wound wa

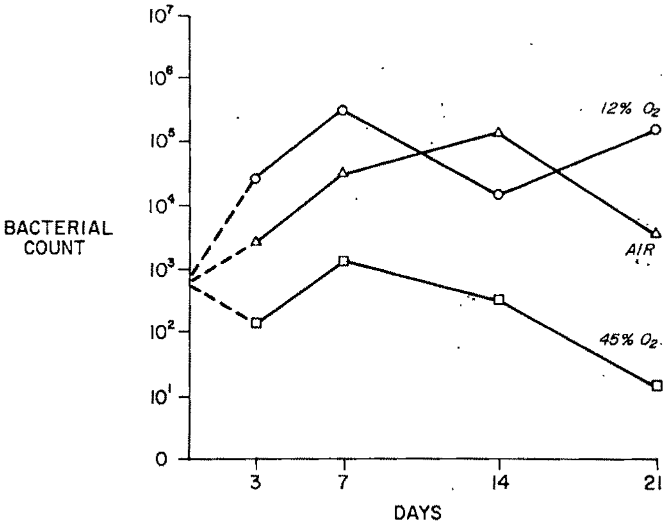

FIG. 1. Mean bacteria count of wounds originally inoculated with 10 bacteria.

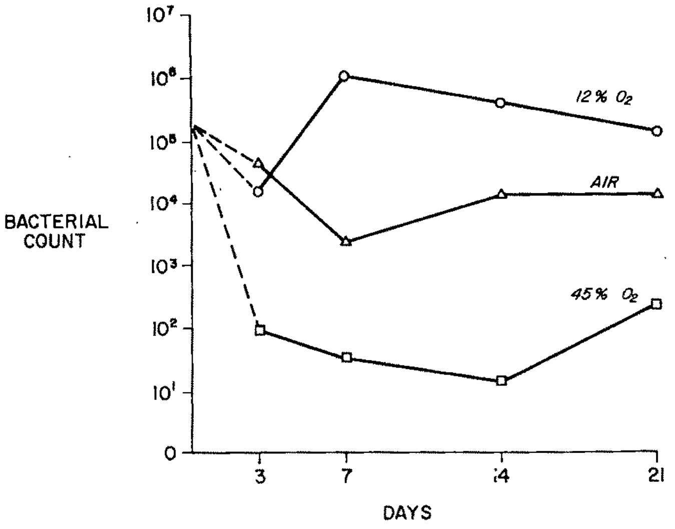

FIG. 2. Mean bacteria counts of wounds originally inoculated with 1(bacteria.

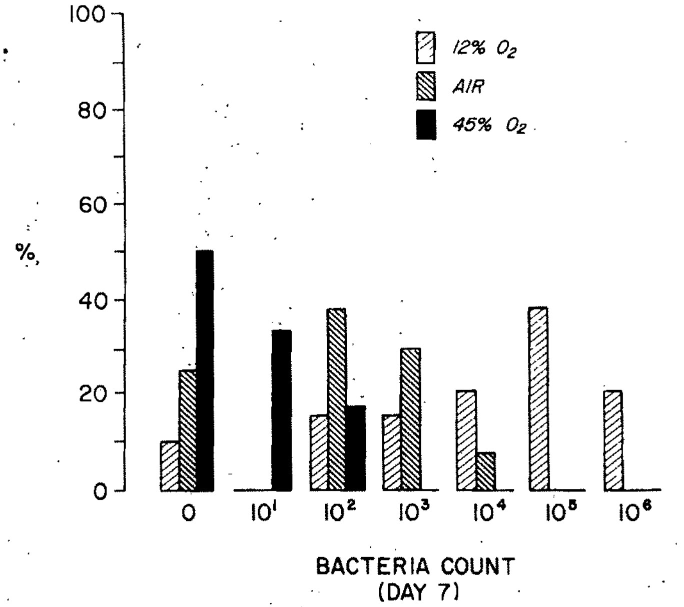

FIG. 3. Percentage of wounds with given breathing gas vs. bacteria count (10^6 bacteria inoculated). Distribution of bacteria counts on day 7 between the three groups. The medians of the hyper and hypoxic groups are more than 1 log apart from the air group.

considered to harbor an established infection when any two of the four samplings had a bacteria count greater than 5×10^2. When this criterion was adopted, as shown in Table 1, a ratio of infected to non-infected wounds could be constructed.

In no case was a control wound infected by any criterion, therefore, cross contamination was not a significant experimental problem.

The respiratory gas tensions in arteries and wounds at the time of inoculation are shown in Table 2. These values were determined in a separate group of animals studied concurrently and kept in identical environments as described above.

Discussion

Previous research on infection and its relation to tissue oxygenation has been performed almost entirely with intermittent hyperbaric oxygen. Oxygen at high partial pressure inhibits growth of some aerobic and anaerobic organisms in culture,[5] but the tensions to which bacteria were exposed in such experiments far exceeded those likely ever to be reached in tissue. Survival time of mice with pneumococcal septicemia was prolonged when they were treated with hyperbaric oxygen shortly after intraperitoneal contamination.[17] Hyperbaric oxygen applied continuously to the surface of experimental wounds infected with *Staphylococcus aureus* or *Pseudomonas aeruginosa* inhibited bacterial growth, but the effect seemed to cease as soon as the treatment was stopped.[10]

Several reports have now documented resolution of chronic osteomyelitis in both animals and man after intermittent hyperbaric oxygen therapy.[18,20]

A mixed result was recently obtained when hyperbaric oxygen was used to treat experimental staphylococcal osteomyelitis. In the animal model tested, the incidence of acute osteomyelitis was unchanged, but accelerated healing of established infections was noted.[7] On the other hand, hyperbaric oxygen failed to alter survival rates in dogs with gram negative peritonitis.[15] In another study, hyperbaric treatment actually seemed to increase the mortality from staphylococcal peritonitis in rates.[6]

Hyperbaric oxygen can be given only intermittently because exposure to hyperbaric oxygen pressures for more than a few hours has toxic effects on the host. We have shown in unpublished studies, there is also a risk of local acidosis from extreme hyperoxia. On the other hand, continuous, relatively mild hyperoxygenation increases wound pO_2 to a lesser degree, but the effect can be maintained indefinitely without progressive wound acidosis or host toxicity.

The present study is unique in that it involved continuous exposure to only 45% oxygen at one atmosphere and specifically investigates both the susceptibility of soft tissue wounds to infection as well as their ability to clear established infection. Furthermore, the techniques used allow us to measure the actual wound environment and relate it to infectability.

These experiments seem to indicate that resistance to in-

TABLE 1. *Ratios of "Infected" to "Uninfected" Wounds Using the Arbitrary Criteria for Infection as 5 × 10² Bacteria or More in 2 of the 4 Samplings*

Large Inoculum	Hyperoxia	0/12 = 0%	Sign.	$p < .015$	$p < .012$
	Normoxic	7/11 = 64%	NSD.	$p < .27$	
	Hypoxic	7/10 = 70%			
Small Inoculum	Hyperoxic	0/18 = 0%	Sign.	$p < .05$	$p < .04$
	Normoxic	5/19 = 26%	NSD.	$p < .28$	
	Hypoxic	4/12 = 33%			

TABLE 2. *Wound pO_2, pCO_2 and pH on the Day of Inoculation (See Methods)*

Blood Gasses At Time of Inoculation			
	PaO_2	$PaCO^2$	PaH
Hyperoxia	191 ± 20	62 ± 8*	7.32 ± 0.02
Normoxia	69 ± 6	31 ± 3	7.46 ± 0.02
Hypoxia	39 ± 2	26 ± 2	7.39 ± 0.02
Wound Gases At time of Inoculation			
	pO_2	pCO_2	pH
Hyperoxia	13.6 ± 0.9	85.6 ± 4	7.19 ± 0.01
Normoxia	10.6 ± 0.7	67 ± 2	7.20 ± 0.01
Hypoxia	6.2 ± 0.4	55 ± 2	7.11 ± 0.02

fection in the wound is oxygen dependent. However, the mechanism is not readily apparent. The variations in wound environment between hypoxic and hyperoxic animals in this study are relatively small. The difference between the normoxic and hyperoxic environments is no greater than 100 mm Hg, and pseudomonas are not inhibited by partial pressures of oxygen up to 760 mm Hg.[5,16] The decreased susceptibility to infection of the hyperoxic group, therefore, must be related to a host factor.

We cannot exclude the possibility that the relative "maturity" of the hyperoxic wounds enhanced resistance. Reciprocally, the "immaturity" of the wounds in the hypoxic group may have contributed to susceptibility. Investigation of this possibility is being carried out. However, the role of "maturity" of the wound in resistance to infection is unclear. All that can be said is that in some way, "mature" granulation tissue seems quite resistant to infection.

The most likely explanation for our findings seems to be found in the reaction of the phagocytic defense system to changes in oxygen environment. White cells ingest bacteria in a wide variety of environments, even anaerobic ones. However, phagocytosis of bacteria by polymorphs is followed by a burst of oxygen consumption which seems to be important to intracellular killing.

Neutrophils derive energy for particle ingestion from glycolytic metabolism.[3,11,13] Inhibitors of oxidative pathways, such as cyanide and hypoxia do not inhibit particle ingestion *in vitro*.[3,18] Killing of ingested organisms on the other hand, is greatly impaired under anaerobic conditions. For instance, Cline has shown that intracellular killing of Listeria by human macrophages is diminished by one-third when the pO_2 of the medium is changed from greater than 100 mm Hg to less than 15 mm Hg.[3] The pO_2 of wound dead spaces after the first few days is below 10 mm Hg.

The burst of oxygen consumption following phagocytosis is associated with greatly increased glucose oxidation through the hexose monophosphate shunt. Thus, the leucocyte is able to switch from anaerobic to aerobic conditions after phagocytosis, provided oxygen is available.[1,13]

Hypoxia reduces resting oxygen consumption of guinea pig monocytes and polymorphonuclears as shown by Stähelin, Sutter and Karnovsky.[21] They showed oxygen consumption fell by more than 80% when pO_2 of the medium was reduced from 150 to 8 mm Hg. They also noted that oxygen consumption, lactate production and viability of polymorphonuclears fell considerably as pH fell below 7.5, although monocytes were not as severely affected. In the present experiments, wound pH fell from a control level of 7.2 to less than 7.1 in hypoxia and rose slightly with the hyperoxic environment. Kempner also has reported the depressed resting respiration by leukocytes subsequent to lowered oxygen tension.[12]

The enzyme system which relates to intracellular killing is extremely complex. In general, however, investigators agree that the production of hydrogen peroxide and the reduction of NADPH by the NADPH oxidase system with the aid of a halide ion is a major component of the killing mechanism.[11,14] Allen, Stjernholm, and Steele have demonstrated that the active principle in the peroxide reaction is derived from atmospheric oxygen.[1] Therefore, the system would seem to be pO_2 dependent. Furthermore, sepsis of several types has been related to white cells which are myeloperoxidase deficient. Furthermore, the often fatal chronic granulomatous disease is apparently due to a failure of the peroxide producing mechanism.[11] Thus, there is considerable circumstantial evidence indicating that the hypoxia which characterizes injured tissue may well be responsible for the concomitant increased susceptibility to infection.

One can hypothesize that bacteria, fibroblasts, and phagocytes compete for what little oxygen is available in the wound space. Infection results when sufficient bacteria are present to overwhelm the phagocytic response or to diminish its already poor oxygen supply to the point that intracellular killing becomes insufficient to prevent infection. Provision of extra oxygen in the normally hypoxic wound apparently enhances phagocytic killing. Hypoxemia in addition to the normal wound hypoxia probably puts the phagocytic response at a further disadvantage.

This project was undertaken to investigate a possible mechanism for the increased infectability of wounds in trauma patients. It was intended to extend Conolly's experiment in which he showed that remote trauma (which diminishes wound oxygen supply) doubled wound infectability.[4] The wound pO_2 produced in the present experiment by hypoxemia was designed to be the same as that produced by remote trauma. Inocula and organisms were identical with the previous study. However, where the infection rate was doubled by trauma, it rose only about 40% in the current study. The reason for this difference may be apparent in the wound gas data. The effect of remote trauma is to diminish would perfusion, to decrease pO_2, but also to *increase* pCO_2 in the wound by diminishing the means of its removal.[22,23] Pure hypoxia without hypoperfusion ***decreases*** pO_2 but also *decreases* pCO_2. Thus, hypoxia is not the equal of hypoperfusion. Of the two, hypoperfusion seems the most powerful potentiator of infection. This observation correlates with those of Siegel, Goldwyn, and Friedman who noted that the highest mortality rates in sepsis occurred in those patients whose mixed venous pCO_2 was markedly elevated.[19].

Because of the recent discovery that enhanced oxygen delivery can accelerate healing in both soft tissue and bone[8] we have been tempted as has Hamblen[7] to conclude that the cure of chronic osteomyelitis with hyperbaric oxygen is merely a result of enhanced healing. The present study suggests, however, that enhancement of phagocytic killing of bacteria may be part of the mechanism.

It would seem a simple matter to advocate that enriched oxygen mixtures be given to all patients at risk for wound infection since we have shown in unpublished studies that breathing oxygen elevates wound pO_2 in humans. In practice oxygen breathing can enhance tissue oxygenation; but it will do so only if blood volume is maintained, if vasoconstriction is minimized, if blood supply is adequate, and if fluid overloads and tissue edema are avoided. If tissue oxygen transport is kept normal, however, hyperoxia could possibly become a practical method of enhancing resistance to infection in otherwise susceptible wounds. Certainly, the avoidance of hypoxia and hypovolemia would seem important in prevention of infection.

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Vagotomy and Double Pyloroplasty for Peptic Ulcer

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Seventy patients with peptic ulcers (55 duodenal and 15 gastric) were treated by truncal vagotomy and double pyloroplasty during the past four years. Clinical and experimental data as presented lead us to believe that transecting the pylorus twice produces an incontinent pyloric sphincter and a larger gastric outlet than is found in other methods of pyloroplasty. This decreases gastric stasis and has led to a lower ulcer recurrence rate (1.5%). In addition, the untoward postoperative sequelae are minimal. The 70 patients treated (for the most part consecutive cases) exhibited the usual complications of peptic ulcer disease. Thirty-three had intractable pain, 23 bleeding (15 massive), 13 obstruction, and one acute perforation. There were no operative or postoperative deaths and the only serious postoperative complication was unrelated to the double pyloroplasty. During the followup period four patients have died of unrelated diseases. Of the remaining 66 patients one developed a probable recurrent peptic ulcer which has responded to medical management. Four patients have intermittent dumping, three have mild diarrhea and one has failed to gain weight. Constipation and weight gain are more common complaints. It would appear that vagotomy with double pyloroplasty is a safe and effective operation for peptic ulcers and that further clinical trials are warranted.

WE FEEL that most failures (following vagotomy and pyloroplasty for peptic ulcer) are due to poorly emptying pyloroplasty. If you have a stomach that does not empty, you are in trouble . . . and so is the patient!" (Jack M. Farris, commenting on Hoerr and Ward.[27])

While attending a lecture on rectal surgery, one of us (J.H.) was again impressed by the admonition that the anal sphincter can be safely transected once but that double transection leads to rectal incontinence. This led to the speculation that double transection of the pyloric sphincter might be utilized to produce pyloric incontinence as an adjunct to pyloroplasty, hopefully to improve gastric emptying.

A wide variety of surgical procedures have been advocated for the treatment of peptic ulcer disease during the past 25 years. Operations that preserve gastric tissue have earned an increasing popularity. Vagotomy with pyloroplasty has become the most widely used primary surgical treatment in peptic ulcer disease.[30,48] The major obstacle to the general acceptance of this procedure has been a distressingly high ulcer recurrence rate of 4–27%. In addition, the unpleasant side effects of dumping, diarrhea, and failure to gain weight have not been eliminated.[18,19,25,31,42,56]

The causes for recurrent ulcer following vagotomy and drainage include gastric stasis due to inadequate drainage procedures, incomplete vagotomy, and undiagnosed Zollinger-Ellison tumors.[30] A wide variety of gastric outlet procedures, such as the Weinberg modification of the Heineke-Mikulicz pyloroplasty, the Finney pyloroplasty, and the Jaboulay gastroduodenostomy have been used in an attempt to improve gastric emptying. Selective vagotomy has many advocates who feel that it affords a more complete vagotomy than truncal vagotomy. In this procedure the nerves to the stomach are divided while the nerves to the other viscera are preserved. It is usually accompanied by an outlet procedure. Highly selective (parietal cell mass) vagotomy has also been used. In this procedure the parietal cell mass of the stomach is deprived of its vagal innervation, while the nerves of Laterjet, the nerves to the antrum, and the remaining vagus nerves are preserved. The pyloric sphincter remains functional so that an outlet procedure is usually not needed. Recent studies of patients that have had parietal cell mass vagotomy indicate that over a period of two or three years there may be some parasympathetic regrowth as the insulin and histamine stimulation tests tend to show an increased response.[60] The Zollinger-Ellison Syndrome is now more frequently recognized as there is increased awareness of its hypersecretion, hyperacidity, and elevated serum gastrin levels.

Our personal observations have led us to believe that the

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high recurrence rates observed following vagotomy and gastric outlet operations are usually related to a poorly functioning gastric outlet procedure. Even the single layer Weinberg modification of the Heineke-Mikulicz has been shown to result in gastric stasis.[30,39,40,55] We have developed a new gastric outlet operation that has greatly improved gastric emptying. It is the purpose of this paper to describe the rationale of this procedure and to report the results of early clinical trials.

Background

Gastric Innervation

The *sympathetic* innervation of the stomach is through the paired T_5 through T_{10} sympathetic ganglia via the greater and lesser splanchnics, the celiac plexus, and the right and left celiac and the superior mesenteric ganglia. The post ganglionic fibers are conveyed to the stomach alongside the celiac and superior mesenteric arteries. Historically, the removal of the sympathetic ganglia (as in the Smithwick operation for hypertension) caused parasympathetic overbalance with gastric hyperacidity, hyperperistalsis, and pyloric relaxation. These patients had an unusually large number of peptic ulcers. The ulcers were almost always painless, the primary symptoms being bleeding, perforation, or obstruction.

A complete vagotomy (in the presence of intact sympathetics) results in a sympathetic overbalance with hypoacidity, gastric atony and hypertonicity of the pyloric sphincter. Removing the vagal innervation of the stomach results in two defects: the loss of the antral pump and pylorospasm. As far as the remainder of the intestine is concerned, a complete vagectomy *should* result in constipation, not diarrhea. It is possible that "post-vagotomy" diarrhea may be due to incomplete vagectomy and with overstimulation of the remaining fibers of the vagus. It is our impression that a complete truncal vagotomy at the esophago-gastric junction not only produces anacidity but usually leaves the patient with either normal stools or somewhat constipated. We have continued to perform truncal or "total" vagotomy and have directed out investigational efforts toward an improved gastric outlet procedure. We designed studies to see if the pyloric sphincter becomes incontinent when transected twice, and to determine how this affects gastric emptying.

Experimental Studies

Cadaver Studies

Studies were carried out on ten cadavers. We found that the posterior aspect of the human pylorus could be transected without endangering the common bile duct, the pancreas, or other vital structures. Even in patients with scarring from peptic ulcer disease the posterior sphincter could be safely transected.

Dog Experiments

Twelve healthy, large adult mongrel dogs were kept on a standard laboratory diet and received the usual inoculations. Four dogs were used as controls. Four dogs had a bilateral truncal vagotomy and a Weinberg modification of the Heineke-Mikulicz pyloroplasty. In the remaining four dogs a back wall pyloric transection was added to the vagotomy and Weinberg pyloroplasty (Fig. 1). Gastric emptying times were studied two months after the operation by feeding the dogs a mixture of 60 gm of barium sulfate, 200 gm of canned dog food and 50 cc of water and taking hourly films until the stomach was empty. The emptying times in all three of these groups were not statistically different, having 75% emptying in 5–5½ hours and complete emptying in 7–7½ hours. (We should have repeated these emptying studies at longer periods following operation, as later human studies showed that after a year patients with a double pyloroplasty emptied better). The eight dogs with vagotomy and pyloroplasty were re-operated at four months. The animals with a double pyloroplasty had an "incontinent" sphincter, as it did not completely close on stimulation. The pyloric openings were then measured by a modification of a "ring-sizer" dilator. On modest pressure the dogs with a double pyloroplasty had a 25% larger gastric outlet. On maximal pressure, the size of the openings in the

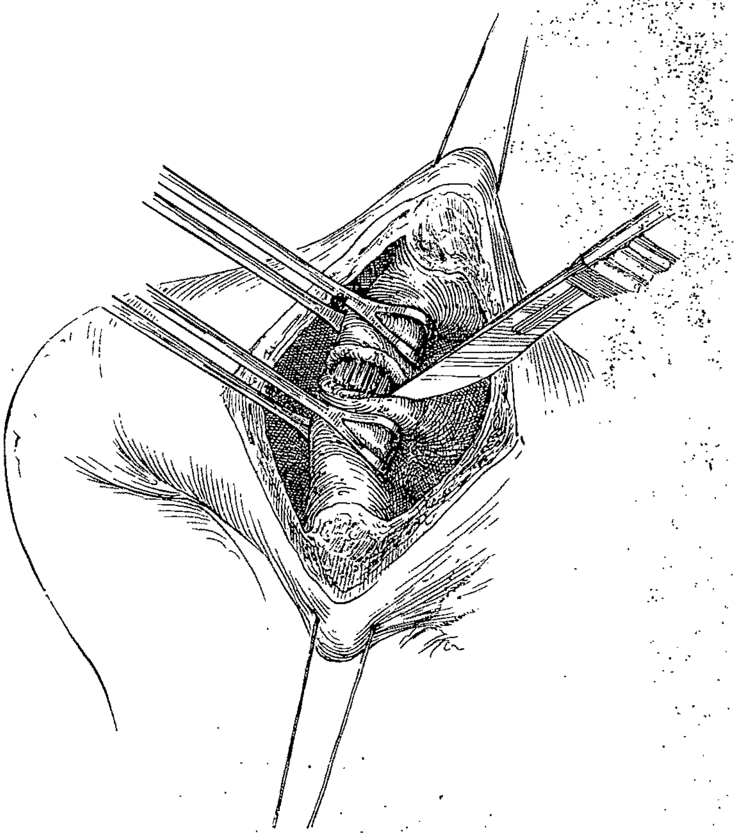

Fig. 1. Method of transection of the posterior pyloric muscle.

two groups were about the same, the difference being related to the size of the animal. None of the dogs had gross evidence of gastritis from duodenal reflux, but microscopic sections were not studied. All of the dogs tolerated the operations without difficulty.

Clinical Studies

During the past four years we have operated upon 70 patients for peptic ulcer disease using a truncal vagotomy and a double pyloroplasty. We made no attempt to eliminate difficult or complicated cases, the 70 cases being consecutive cases operated for both duodenal and gastric ulcers, except in those few cases that pathologic process made the procedure technically impossible. These include delayed perforations, severe inflammatory response, necrotic tissue, or the inability to rule out gastric carcinoma. We have not used this procedure in patients with "stress" ulcers.

Operative Technique

Vagotomy. The bilateral truncal vagotomy was carried out at the esophago-gastric junction, being careful to transect all fibers entering the stomach. Special care was taken to transect a common left lateral branch of the left vagus as it enters the top of the stomach. No attempt was made to preserve any vagal fibers, thus producing a "total" vagotomy. We avoided dissection at the esophageal-diaphragmatic hiatus as we feel that damage to the phrenico-esophageal ligament can lead to reflux esophagitis and at times to iatrogenic hiatus hernia.

Double Pyloroplasty. This technique was first described by one of us (J.H.) in Surg. Gynecol. Obstet. in July, 1971. It consists of the Weinberg modification of the Heineke-Mikulicz pyloroplasty with the addition of a posterior wall transection of the circular pyloric muscle (Fig. 1). After transecting the posterior pyloric muscle, the mucosa and submucosa were closed. A Kocher maneuver was carried out in order to close the anterior suture line without stress. Through the anterior pyloromyotomy gastric ulcers were biopsied and actively bleeding ulcers oversewn. In patients with post-bulbar stenosis the opening on the gastric side was made near the pylorus and the opening on the duodenal side was carried down to a point distal to the stenotic area. Post-bulbar stenosis was easily treated by this method. The index finger was introduced into the duodenum in *all* cases to eliminate the possibility of post-bulbar duodenal stenosis.

Patient Population

All 70 patients were operated upon in the Wesley Pavilion of the Northwestern Memorial Hospital, a 650-bed private practice hospital associated with Northwestern University Medical School. Fifty-two patients were private patients and 18 were service or clinic patients. The ages varied 17–73 years and the average age was 48 years. Forty-eight were males and 21 were females. Fifty-one were white, 18 black, and one Oriental. The duration of symptoms was from 2 days to 38 years, and the average duration was 8½ years. Eighteen patients had serious associated medical illnesses; diabetes, pulmonary disease, alcoholism and drug abuse being among the most common of these diseases.

Location of Ulcers

Fifty-five patients had duodenal ulcers and 15 gastric ulcers. Of the 55 duodenal ulcers 48 were in the bulbar region and seven were in the post-bulbar area causing post-bulbar stenosis. Of the gastric ulcers two were multiple, four were pre-pyloric or channel ulcers and the remaining nine were single gastric ulcerations of varying size. All patients with gastric ulcers had gastroscopy with biopsy of the ulcers as well as repeated biopsies at the time of the operation. None of the patients with gastric ulcers has developed a carcinoma, has had an overlooked carcinoma, or has failed to heal. Improved gastroscopy with biopsy has been especially helpful in establishing the correct diagnosis prior to the operation (Table 1).

Reason for Operation

Thirty-three of our patients were operated upon for intractable pain, 23 for bleeding, 13 for obstruction, and one for acute perforation. Of the 33 patients operated primarily for pain, eight also had bleeding episodes. Seven of those patients also had severe weight loss. Of the 23 patients operated upon for bleeding, 11 were operated upon during an acute massive hemorrhage and had the bleeding point oversewn. Four were operated upon after the acute massive hemorrhage had stopped. Massive bleeding is arbitrarily described as bleeding that requires replacement of 2,000 ml of blood in 24 hours or 3,500 ml in 72 hours. Eight patients were operated upon for repeated hemorrhages. Of the 13 patients operated upon for obstruction, three were obstructed from recent perforation, two were obstructed from acute channel ulcers, and the remaining six had progressive obstruction from old scar tissue. We were somewhat reluctant to use this procedure in patients with obstruction but early success encouraged its use. One patient with an acute perforated duodenal ulcer was treated by vagotomy and double pyloroplasty (Table 2).

TABLE 1. *Location of Ulcers*
(70 Patients)

Duodenal			55
	Bulbar	48	
	Post-bulbar	7	
Gastric			15
	Single	9	
	Multiple	2	
	Pre-pyloric or Channel	4	

TABLE 2. *Reason for Operation*
(70 Patients)

Pain			33
Bleeding	Massive	15	23
	Repeated	8	
Obstruction	Chronic	7	13
	Acute	6	
Perforation	(Acute)		1

Preoperative Evaluation

Most of the patients operated upon had basal acid studies, response to insulin and histamine, gastric volume studies, and upper G.I. exams. In the case of acute bleeding or in gastric ulcers, gastroscopy, biopsy, and at times, angiography were performed. During the past few years endoscopy has become about 90% accurate compared to an average of 75% in upper gastrointestinal X-rays. The combination of both studies gives excellent results.

Results of Clinical Studies

Intraoperative Problems

Vagotomy. The complications of this procedure are usually minimal. Esophageal damage is rare but temporary dysphagia has been reported to be as high as 5%.[47] This may have played a role in a patient that developed esophageal obstruction from a bolus of meat. Two patients in our series required splenectomy because of capsular bleeding.

Pyloroplasty. We have had no suture line difficulties using the Weinberg modification of the Heineke-Mikulicz pyloroplasty in some 200 cases in our personal series. In addition, we have had no problems related to the posterior wall procedure in the 70 cases reported in this series. We feel that the Kocher maneuver reduces the stress on the suture line and is of value.

Multiple Procedures. In the current series we have performed gastric biopsy in 11 patients, oversewing the bleeding areas in 11 patients, cholecystectomy in six patients, and repair of a hiatus hernia in two patients.

Immediate Postoperative Period

Because of the Weinberg closure there is often some postoperative bleeding from the mucosal margin; this rarely exceeds 200 ml and usually stops within 12 hours. Ten patients developed atelectasis which responded promptly to treatment. Two patients, both of whom had chronic obstructive pulmonary disease, developed pneumonitis. One patient developed gastric atony which required a nasogastric tube for eight days, one patient had an ileus that required decompression for 12 days, and one patient had a partial small bowel obstruction that needed decompression for 14 days. One patient swallowed an unchewed bolus of meat which caused an incomplete obstruction at the esophago-gastric junction. An attempt at extraction on the 12th postoperative day resulted in esophageal perforation that required both abdominal and thoracic drainage and six weeks of postoperative hospitalization. She eventually made a complete and total recovery and is without symptoms. Three patients developed urinary tract problems that responded to treatment. Five patients developed superficial would infections, and the organisms cultured would indicate their origin to be the patient's skin or the nasopharynx of the operating team. Because of the larger opening produced by the double pyloroplasty, the nasogastric suction was usually removed 24–48 hours after operation. We feel that the early removal helped to reduce pulmonary problems and encouraged early ambulation.[43] Feeding of liquids was usually started on the third or fourth day. Most patients were discharged on the seventh or eighth postop day.

Long Term Postoperative Followup

The method of postoperative evaluation was by individaul person-to-person interview. The patients were given ample opportunity to discuss their symptoms or related problems. All of the patients were followed. The average period of followup was 22 months. Seven patients had mild diarrhea that persisted for three months and then stopped. Three other patients continue to have at least one loose stool a day, but the diarrhea is not debilitating. Five patients complain of constipation and in one patient this has been a serious problem. One patient had lost weight preoperatively from 170 to 135 pounds. For the next 18 months he was unable to gain weight. He finally gained to 160 only to develop a squamous cell carcinoma in his neck and back down to 120 pounds. This is the only patient who failed to thrive. Weight gain, not weight loss, became a common problem, as serious obesity has developed in four patients. Seven patients described the "dumping syndrome" of post-cibal epigastric distress, palpitation, and sweating, these symptoms being relieved by lying down. In three patients this has disappeared but it has persisted more than a year in four others. In most of these patients it is sporadic and is partially relieved by eating dry meals. All of the 13 patients operated upon for obstruction were carefully followed with upper gastrointestinal X-rays. None of these patients has re-obstructed. One patient with a huge stomach required seven months before his stomach returned to a normal size as seen in serial gastrointestinal studies. During this period he was symptomless. One patient was seen a year after having been operated upon for obstruction with the complaint of two black stools following a weekend of excessive alcoholic intake. She recovered without treatment and was thought to have had alcoholic gastritis, but this could not be documented as she refused examination or treatment. One patient developed epigastric pains 2½ years after his operation. Six months later a stomach X-ray demonstrated a possible pre-pyloric antral recurrence, but this was not confirmed by gastroscopy. He was put on medical management and has been symptomless for six months. While our period of followup is short (6 months to 3½ years), Hoerr & Ward report that recurrent ulceration severe enough to require another operation usually manifests itself within three years.[27,57] The other untoward postop problems usually appear immediately after surgery, and only infrequently later on[44] (Table 3).

Postoperative Studies

Thirty-seven patients in this series had upper G.I. X-rays taken from two weeks to two years following their operation. One-hour emptying times were studied. Radiologically it would appear that patients with a double pyloroplasty have a larger opening than patients with the Weinberg modification of the Heineke-Mikulicz pyloroplasty. Within the first few months following the operation, the gastric emptying times following barium meal were about the same in both groups. However, when emptying times were studied a year or more after operation, the patients with double pyloroplasty appeared to empty more readily than those with a single pyloroplasty.

Deaths

Four patients have died since having had a vagotomy and double pyloroplasty; however, the deaths were not related to the operation or to peptic ulcer disease.

Current Status of Patients

Of the 66 surviving patients, only one had developed suspected recurrent peptic ulcer disease. Eight patients have symptoms relating to their ulcer surgery: one failing to gain weight; four have mild dumping, and three have moderately loose stools. In addition, five patients complain of constipation and four of obesity.

As to patient satisfaction, two patients, the one with the possible recurrence and the patient with esophageal perforation, were not pleased to have had the operation (Table 4).

Discussion

Subtotal gastrectomy still has some proponents as the primary form of treatment for peptic ulcers.[46] Under ideal circumstances this surgery can be performed with a low operative mortality and morbidity rate and it has a low recurrence rate. The slightly higher mortality rate and the undesirable side effects have urged surgeons to seek other procedures.[17,31,62] Truncal vagotomy with antrectomy has a low operative mortality and morbidity rate, a low rate of disabling side effects and a very low rate of recurrence. It is the procedure of choice for a large number of surgeons.[18,19,25,31,42,47,50,56,65] Selective vagotomy with antrectomy has many advocates who feel that this procedure produces a more complete vagotomy with fewer untoward postoperative sequelae and a lower recurrence rate.[22,32,33,36,52,53] Other authors feel that there is little difference between the results obtained between selective and truncal vagotomy and that selective vagotomy must be approached with caution.[10,28,31,35,38,44,55,59]

Truncal vagotomy with gastrojejunostomy is employed infrequently because the postoperative diarrhea, dumping and recurrence rates are high.[2,20,52,60,64] Its use now is usually confined to those few cases in which there is a marked inflammatory response that precludes other operations.

Truncal vagotomy with pyloroplasty is currently the most widely used procedure in patients with duodenal peptic ulcers. The ease of performance gives it a low operative morbidity and mortality. The untoward postoperative sequelae is minimal, and the recurrence rate is acceptable, although higher than with vagotomy and antrectomy.[18,19,25,31,42,56] Vagotomy and pyloroplasty has recently been reported to be satisfactory in patients with obstructing duodenal ulcers.[9] Some authors feel that this procedure can cause an abnormally rapid emptying time which leads to diarrhea or dumping.[6,7,29,33,45] Selective vagotomy with pyloroplasty has many advocates; other surgeons have reservations about this procedure and suggest that it may lead to more difficulties.[10,28,38,42,59] Most surgeons prefer the Heineke-Mikulicz pyloroplasty or the Weinberg modification,[24,27,30,31] while others prefer the Finney[9,27,34,60] and some the Jaboulay.[15,30,52]

Highly selective vagotomy without drainage has been used in patients without gastric outlet problems. In those patients the operative morbidity and mortality have been low and the side effects and recurrence rates minimal.[1,4,5,21,28,33,34,59,60] Studies have shown dumping to be present but infrequent[58] and recurrence has been uncertain.[60] This method deserves further study because it does not require opening into the gastrointestinal tract and has the promise of a low incidence of dumping and diarrhea.[28,44] The obvious hazard of vagotomy without drainage is that of delayed

TABLE 3. *Late Postoperative Problems*
(70 Patients)

Constipation	5
Obesity	4
Dumping (Mild)	4
Diarrhea (Mild)	3
Bleeding (Following Debauch)	1
Probable Recurrence	1

TABLE 4. *Current Status of Patients*
(70 Patients)

Died of unrelated diseases	4
Post-prandial distress (mild)	7 of 66
Probable recurrence (now symptomless)	1 of 66
Patient satisfaction	64 of 66
Average period of followup	22 months

outlet obstruction. Some form of transection of the pylorus may be important as some investigators have suggested a relationship between peptic ulcer disease and pyloric hypertrophy. They are unsure whether the pyloric hypertrophy preceded or was caused by the ulcer.[13,14,49] Johnston and Goligher suggest that perhaps the selection of the type of vagotomy and pyloroplasty is less important than the skill of the surgeon.[32]

The surgical treatment for patients with *gastric* peptic ulcers is controversial, and most authors recommend gastric resection.[63] Recently some surgeons have found vagotomy and drainage to be unsatisfactory.[51] This problem needs to be totally reviewed.

We have compared the recurrence rate in the current series (1.5%) with the recurrence rate in a retrospective study of 70 patients that we operated upon at an earlier time using vagotomy and a Weinberg pyloroplasty. In the early group seven recurrences (10%) occurred during a similar period of observation. The improved results realized in the later series may have been due to the double pyloroplasty; other factors, however, must be considered. Diets are more realistic, practical and easier to follow, and patients are more strictly admonished to avoid alcohol, tobacco, caffeine, salicylates, steroids, and anti-cholinergic drugs. A more complete vagotomy may have been achieved by further experience. Awareness of gastrin-producing tumors has decreased the chance of overlooking this diagnosis. A last factor is most difficult to evaluate: when an investigator takes a special interest in any field his attention to detail often leads to better results, whether or not the results are related to the new procedure or treatment. This was clearly pointed out by Dr. Francis Moore in an editorial related to new methods of burn therapy.[44] In spite of these possibilities we feel very strongly that the method of pyloroplasty we used greatly reduced gastric stasis and reduced the rate of ulcer recurrence.

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Pancreatic Exocrine Secretion During and After Pregnancy

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Pancreatitis occurring in late pregnancy and in the puerperium has been documented as an entity unrelated to cholelithiasis or hyperlipidemia. Canine pancreatic exocrine function has been studied during pregnancy and the puerperium. Pancreatic secretion was evaluated in eight pregnant female mongrel dogs prepared with Thomas duodenal and gastric fistulae, during pregnancy (corresponding to the third trimester in humans), during the puerperium, and several months after whelping. Basal secretion (volume and HCO_3) was increased during pregnancy and the puerperium. The response to exogenous secretin (submaximal and maximal) was unchanged during pregnancy but decreased in the puerperium. Resting enzyme output was increased during pregnancy and the puerperium; the responses to cholecystokinin-pancreozymin during pregnancy were even more profoundly increased. Although the mechanism is speculative, these alterations in pancreatic function might contribute to the development of pancreatitis in pregnancy and the puerperium.

PANCREATITIS occurring in late pregnancy and in the puerperium is a well recognized entity.[5,7,9] Cholelithiasis[14] and hyperlipidemia[1,10] have been invoked as etiologic factors in many cases, but in a number of instances no etiologic factors are apparent and the pathogenesis is poorly understood. Little information is available on pancreatic secretion during pregnancy. In the present study we report on alterations in pancreatic exocrine function during pregnancy and the puerperium.

Methods

Eight pregnant (3–4 weeks pregnant) and three nonpregnant female mongrel dogs weighing 17–22 kg were prepared with Thomas cannulae[15] in the duodenum opposite the major pancreatic duct; the accessory duct was ligated and divided. In two of the pregnant and two of the nonpregnant dogs a gastric cannula was placed in the most dependent part of the stomach and was opened during subsequent experiments to divert gastric acid secretion; this prevented the release of endogenous secretin by acid contamination of the duodenal or jejunal mucosa. Experiments were commenced 7–10 days after surgery.

Each experiment was carried out with the animal in the conscious state, standing quietly in a harness, and deprived of food but not water for at least 18 hours. Animals were studied no more than 2–3 times a week and never on consecutive days. A continuous intravenous infusion of 0.15 M sodium chloride was maintained throughout each experiment to allow for fluid losses. The main pancreatic duct was cannulated under direct vision through the Thomas cannula and the gastric cannula (in some dogs) was opened. Pancreatic secretion was collected at 10 minute intervals in the resting state and 5 minute intervals in the stimulated experiments. The secretory stimulants used were pure natural secretin 1 u/kg (Gastrointestinal Hormone Research Unit, Stockholm, Sweden) and secretin 1 u/kg with cholecystokinin-pancreozymin 1 u/kg (Cecekin, Gastrointestinal Hormone Research Unit, Stockholm, Sweden). In all experiments, both hormones were from the same batches and were administered by single intravenous injections; the order of injections was randomized.

Pancreatic secretion was collected under oil and each sample was individually analyzed for volume, bicarbonate, chloride and protein concentrations, the latter serving as a measure of enzyme secretion. Bicarbonate and chloride con-

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centrations were measured with a Technicon Autoanalyzer and protein concentration was measured by the method of Preshaw *et al.*[12]

The pregnant bitches were studied during a period corresponding to the third trimester in humans, in the early post-partum period and in the late post-partum period The early post-partum period or puerperium was arbitrarily defined as the first three weeks after delivery and the late post-partum period as at least three months after delivery. Control values were taken from the late post-partum period and from the three non-pregnant bitches matched for weight. The non-pregnant group also acted as a further control in demonstrating that pancreatic secretion did not vary in individual dogs during the period of study and that any changes noted were due to the pregnancy. At least three separate studies with each stimulant were obtained.

Results

It was not always possible to obtain the pregnant dogs at the optimum time. Two dogs were nearer term than expected and delivered soon after surgery so that they could not be studied during pregnancy; these were studied only during the puerperium and the late post-partum period.

Electrolyte Secretion

Basal (Table 1). The resting secretion in the control animals (non-pregnant) was identical to that of the animals studied in the late post-partum period. These results are combined and presented in this and in subsequent tables as control values. Mean basal volume was 0.85 ± 0.07 (S.E.M.) ml/10 min during control studies. A significant increase in volume ($p < 0.01$) occurred during pregnancy, the rate of secretion rising to 1.87 ± 0.40 ml/10 min. There was a slightly lower rate of secretion in the puerperium (1.74 ± 0.10 ml/10 min) but this was not significantly different from the rate of secretion during pregnancy. The mean bicarbonate concentration of 49.4 ± 2.9 mEq/L rose to 79.5 ± 7.2 mEq/L during pregnancy and 74.6 ± 2.9 mEq/L in the puerperium. Bicarbonate output was increased by 319% during pregnancy and 211% in the puerperium.

Secretin-stimulated. Volumes for the first three consecutive 5-minute periods after injection of secretin were added together and the results are expressed as ml/15 min. Control volumes (Table 2) were no different during pregnancy but were reduced by 22 percent in the puerperium. Bicarbonate concentration of 127.5 ± 1.1 mEq/L was decreased to 121.4 ± 3.2 mEq/L during pregnancy and 119.3 ± 1.9 mEq/L in the puerperium. Bicarbonate output was decreased by 29% in the puerperium ($p < 0.001$). Volume and bicarbonate secretion were similarly affected when secretin was administered in combination with cholecystokinin-pancreozymin (Table 3).

Relation of Bicarbonate Concentration to Volume

In order to investigate the reason for the increased bicarbonate concentration seen in the unstimulated experiments and the decreased concentration in the stimulated experiments, the bicarbonate concentration in all experiments was plotted against rate of flow. The typical hyperbolic relationship between bicarbonate concentration and flow rate was obtained. Analysis of the experiments in which bicarbonate concentration was altered revealed that increases and decreases in bicarbonate concentration were always dependent on similar alterations in the rate of flow.

Enzyme Secretion

Enzyme output in the resting state was increased by 73% during pregnancy and 35% in the puerperium (Table 4). In sharp contrast to electrolyte secretion, the responses to cholecystokinin-pancreozymin was markedly increased during pregnancy but not the puerperium. In some animals the increased enzyme responses persisted during the first post-partum week but this was not statistically significant. It is of interest that the enzyme concentration of resting secretion was unchanged; the increase in output occurred pari passu with the increased volume. Enzyme responses to

TABLE 1. *Basal Volume and Electrolyte Secretion During Pregnancy and Puerperium*

	Volume (ml/10 min)	HCO_3 Concentration (mEq/L)	HCO_3 Output (mEq/10 min)
Control			
Pregnant dogs	0.85 ± 0.08	51.0 ± 3.2	49.8 ± 6.5
Non-pregnant dogs	0.86 ± 0.13	46.6 ± 5.6	44.5 ± 11.3
Total	0.85 ± 0.07	49.4 ± 2.8	47.6 ± 5.7
During Pregnancy	1.87 ± 0.40	79.5 ± 7.2	199.5 ± 50.1
Puerperium*			
Group A	1.64 ± 0.12	71.0 ± 3.9	129.8 ± 19.2
Group B	1.75 ± 0.15	76.6 ± 4.0	158.6 ± 15.9
Total	1.74 ± 0.10	74.6 ± 2.9	148.0 ± 12.3

Mean ± Standard Error.

* Group A refers to dogs studied during pregnancy and puerperium; Group B refers to dogs who delivered before studies could be carried out. Studies were performed in puerperium only.

TABLE 2. *Electrolyte Secretion in Secretin-Stimulated Gland*

	Volume (ml/15 min)	HCO_3 Concentration (mEq/L)	HCO_3 Output (mEq/10 min)
Control			
Pregnant dogs	19.2 ± 0.9	128.0 ± 1.23	2531 ± 131
Non-pregnant dogs	17.8 ± 1.63	126.3 ± 2.2	2268 ± 231
Total	18.82 ± 0.79	127.5 ± 1.09	2459 ± 114
During Pregnancy	17.5 ± 0.98	121.4 ± 3.23	2170 ± 163
Puerperium			
Goup A	13.4 ± 1.26	119.1 ± 3.16	1616 ± 163
Groug B	15.6 ± 1.0	119.4 ± 2.4	1808 ± 112
Total	14.7 ± 0.8	119.3 ± 1.88	1734 ± 93

cholecystokinin-pancreozymin during pregnancy were increased not only in output but also in concentration. Enzyme concentration was slightly increased in the puerperium, but because of the volume reduction no increase in enzyme output occurred.

Discussion

The duration of pregnancy in dogs is about 62 days. It is possible to be certain about pregnancy in the dog only after 3–4 weeks. We were, therefore, able to study pancreatic exocrine function in the last 3 weeks only, a period corresponding to the third trimester of pregnancy in humans.

Our results demonstrate clearly that the basal volume, electrolyte and enzyme secretion are all increased in late pregnancy and in the puerperium (Fig. 1). The response to secretin is unchanged during pregnancy, but is decreased in the puerperium. A striking change is the increase in enzyme secretion in the unstimulated gland in pregnancy and in the puerperium; enzyme secretion in the stimulated gland was increased during pregnancy, but not the puerperium. These changes reverted after three weeks and were completely normal at three months.

Very little information exists on pancreatic function during pregnancy and the reports are seemingly contradictory. Picinelli and Villani[11] stimulated pancreatic secretion in pregnant females with intraduodenal acetic acid (20 ml 3% solution) and noted a slight increase in the concentration of trypsin and lipase from the duodenal aspirate. Fitzgerald,[5] although not studying pancreatic secretion directly, found that the serum amylase and lipase were very low during pregnancy, especially during the first trimester.

Several possible mechanisms may explain the effects of pregnancy on pancreatic secretion. Gastric acid hypersecretion has been described during lactation,[6] but not during pregnancy[2] in the dog. This hypersecretion could result in duodenal acidification and the release of endogenous secretin so that basal (but not maximal) secretion of pancreatic juice would be increased. Two of our dogs were equipped with gastric cannulae in addition to the duodenal fistulae. Diverting gastric acid from the duodenum by opening the gastric cannula did not alter the pancreatic response when the cannula was closed. It is thus unlikely that gastric hypersecretion affected our results. Moreover, if this were the case, it could only explain the increase in the puerperium.

No information exists on the effects of pregnancy on the metabolism of the gastrointestinal hormones. Conceivably, the complex physiologic changes in hormonal balance during pregnancy and the puerperium could affect the catabolism of secretin, cholecystokinin-pancreozymin, gastrin, glucagon, etc., and secondarily, affect pancreatic secretion. Conversely, our results might simply reflect an altered reactivity of the pancreas to secretin and cholecystokinin-pancreozymin.

Direct effects of individual hormones on pancreatic secretion must be considered. Oophorectomy[4] does not alter pancreatic secretion. Nevertheless, Kirdani, Sandberg and Murphy[8] demonstrated that the injection of labelled estriol,

TABLE 3. *Electrolyte Secretion in Response to Secretin With Chloecystokinin-pancreozymin*

	Volume (ml/15 min)	HCO_3 Concentration (mEq/L)	HCO_3 Output (mEq/15)
Control			
Pregnant dogs	20.0 ± 1.1	128.0 ± 1.6	2651 ± 152
Non-pregnant dogs	19.2 ± 2.2	131.0 ± 3.1	2518 ± 244
Total	19.8 ± 1.0	128.6 ± 3.8	2624 ± 130
During Pregnancy	20.5 ± 2.6	121.6 ± 4.4	2509 ± 371
Puerperium			
Group A	12.7 ± 2.6	116.0 ± 8.0	1559 ± 377
Group B	16.6 ± 0.9	119.0 ± 3.8	1987 ± 114
Total	15.1 ± 1.2	118.0 ± 0.9	1823 ± 169

TABLE 4. *Enzyme Output in Resting State and in Response to Cholecystokinin-pancreozymin*

	Enzyme Output	
	Basal (mg Protein/10 min)	CCK-Stimulated (mg Protein/15 min)
Control	Pregnant dogs	370 ± 27.7
Pregnant dogs	± 3.5	
Non-pregnant dogs	42.8 ± 5.2	376 ± 66.9
Total	41.0 ± 2.9	371.2 ± 25.8
During		
Pregnancy	71.1 ± 12.3	576 ± 168.1
Puerperium		
Group A	50.5 ± 6.1	320 ± 61.2
Group B	58.2 ± 4.5	364 ± 56.2
Total	55.5 ± 3.5	346 ± 43.8

estrone, and diethylstilbestrol resulted in a much higher uptake of and retention of radioactivity in the pancreas than in any other organ in the body. They also demonstrated a pancreatic cytosol-binding protein specific for estrogens in dogs, baboons and humans. Thus a binding site for estrogens has been demonstrated in an organ other than the so-called "target" organ. Although the precise cellular source in the pancreas for the estrogen receptor protein has not yet been clarified, some observations indicate that it may be of acinar origin.[16] If estrogens were indeed responsible for the increased enzyme output in our study, this could be a possible mechanism. We studied the effects of estrogen[3] and progesterone[13] on pancreatic secretion, but were unable to detect any effect. It is possible that we were unable to achieve the large amounts of circulating hormones over a prolonged period of time as exists during pregnancy and the puerperium.

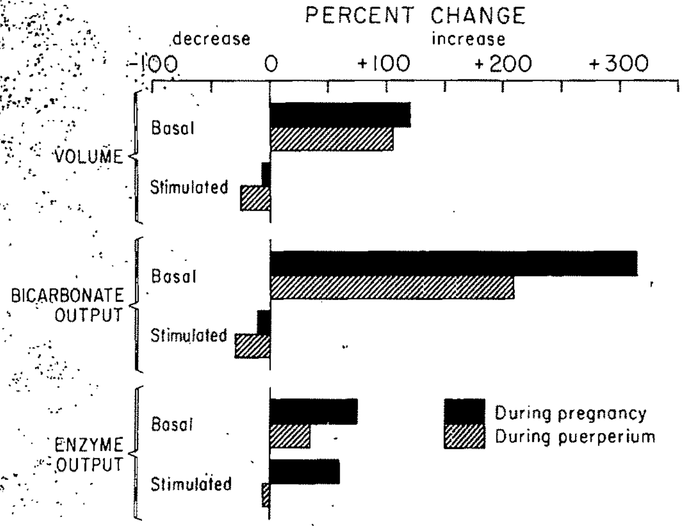

FIG. 1. Per cent change in volume, bicarbonate output and enzyme output during pregnancy and the puerperium.

Caution should be exercised in transposing our data in dogs to the clinical situation. Nevertheless, Joske[7] has drawn attention to the occurrence of pancreatitis during and following pregnancy. This relationship was recorded in 12% of Joske's patients. The symptoms were more likely to occur late in pregnancy[5,7,9] or in the puerperium (so-called "postpartum pancreatitis"). Cholelithiasis, hyperlipemia, or thiazide administration were not common concomitants. In most series of reported cases of acute pancreatitis, pregnancy has seldom been mentioned as an associated condition, but it is recognized as a definite entity. Although the precise mechanism is not clear, the alterations in pancreatic exocrine function we have found could conceivably contribute to the pancreatitis of pregnancy and the puerperium.

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Pulmonary Microembolism Associated With Massive Transfusion:

I. Physiologic Effects and Comparison In Vivo of Standard and Dacron Wool (Swank) Blood Transfusion Filters in its Prevention

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Pulmonary microembolism of microaggregates associated with massive blood transfusion may be a cause of post-traumatic pulmonary embolism. The purpose of this study was to investigate in the dog the influence on certain physiologic parameters of transfusion of blood containing platelet: white blood cell: fibrin (PWF) aggregates and to evaluate the effects of using blood transfusion filters of varying pore sizes during such transfusions. Exchange transfusions of approximately twice blood volume were performed in three groups of animals. Screen filtration pressure measurements verified the presence of large numbers of PWF aggregates in the transfusions. When no transfusion filters or standard commercially available blood transfusion filters of pore size 170 μ were used, experimental animals developed pulmonary hypertension, a decrease in total body O_2 consumption, and metabolic acidosis. Interposition of Dacron wool (Swank) blood transfusion filters prevented these changes.

A NUMBER of abnormalities develop in blood during storage. These include changes in cellular elements and alterations in protein structure and function. Platelets, white blood cells and fibrin (PWF) form aggregates which increase in size and number as storage time increases.[21,26,28,30,31,33-35] Screen filtration pressure (SFP) is an expression of the number of cellular and amorphous aggregates present in blood, and an increase in storage time also causes an increase in SFP of the stored blood.[2,3,7-9,12,21,24-26,30,35]

When blood is passed through Dacron wool (Swank) filters, PWF aggregates are removed and SFP is reduced.[13,19,23,27,30,31] These micro-pore filters have been used extensively to prevent arterial microembolism during extracorporeal circulation.[1,13,34] The prevention of post-traumatic pulmonary insufficiency by using such filters when transfusing to patients large amounts of stored blood has also been reported.[7,27]

It has been verified that following transfusion PWF aggregates collect in the small vessels of the lungs.[7,18,26,33] The purpose of this study was to investigate in the dog the influence on certain physiologic parameters of transfusion of large amounts of blood containing PWF aggregates and to compare the effectiveness of standard blood transfusion filters and Dacron wool (Swank) blood transfusion filters in preventing pulmonary microembolism of such microaggregates.

Methods

Prior to experiments canine blood for transfusion was obtained through a sterile arterial cutdown from donor animals under light sodium pentothal anesthesia. Unlike human blood, canine blood stored in ACD solution does not develop an increased SFP for as long as two months after storage. This was found to be true early in this research and has also been noted by others.[2,3,20,22] When canine blood is stored in heparin however, microaggregates form and SFP begins to rise within two days even though blood clotting has not occurred.[33] For these reasons and in order to insure microaggregate formation, transfusions were collected in standard heparinized plastic bags containing 2250 IU

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heparin (Fenwal JH-IE4R 0603). Bags were filled to 500 cc and stored at 4 C for five days. Platelet and white blood cell counts of each unit of blood were performed on the fresh blood just before storage. Five days later immediately prior to infusion platelet and white blood cell counts were repeated and SFP of each unit of blood was measured using Swank's technique.[8,9,35] No other specific bleeding parameters were studied.

Thirty-two dogs weighing 13–20 kg were anesthetized with an initial dose of sodium pentobarbital, 30 mg/kg. Each animal was then intubated and artificially ventilated with room air using a Harvard respirator set at a tidal volume of 20 cc/kg body weight and 12–15 respirations/min. After cannulating the femoral artery and vein with wide-bore polyethylene catheters, two other catheters were inserted under fluoroscopic control through the right jugular vein into the pulmonary artery (PA) and into the right atrium (RA). Positions were later verified at autopsy in all animals. Muscle relaxation was maintained using pancuronium chloride (Pavulon®), 1 mg/hr.

Each animal's blood volume was calculated as 10% of body weight. Approximately twice this amount of stored canine blood was then administered as an exchange transfusion (Table 1). Infusions in 10 animals (Group NF) were administered using no filter. In 13 other animals (Group CF) a standard commercially available transfusion filter of pore size 170 μ was used (Cutter Saftifilter blood administration set 865-08). In 9 animals (Group SF) a commercially available Dacron wool filter which limits particle passage to those below 15 μ was used (Swank blood microemboli filter, IL-200).[*] Immediately prior to infusion each blood bag was warmed to 37 C in a water bath. It was then thoroughly mixed by gentle agitation and grossly inspected to insure the absence of blood clots. In no experiment was gross blood clot noted in the transfusion filter.

Exchange transfusions were accomplished through the femoral vein catheters with simultaneous removal of the same amounts of blood through the femoral artery catheters. In the experiments in which blood filters were used, no more than 1500 cc of blood were passed through each filter. Using 50 cc syringes, exchange transfusion of 500 cc of blood took approximately 15 minutes. Blood loss due to sampling was added as part of the total amount of blood withdrawn. After each transfusion and before taking samples approximately five minutes were allowed for each animal to stabilize.

PA, RA, and femoral artery pressures were recorded continuously during exchange transfusions and mean PA pressure was calculated as diastolic pressure plus two-thirds of pulse pressure in the PA.

Total O_2 consumption was determined continuously before, during and for 30 minutes after transfusion using an oxygen consumption analyzer (Oxford Instrument Co., Jackson, Mississippi).

TABLE 1. *Mean Amount of Exchange Transfusions and SFP of Stored Blood Before and After Filtration*

	Number Of Dogs	Mean Amount of Blood Infused (ml)	Mean SFP of Blood (mm Hg)	
			Before Filtration	After Filtration
No filter (Group NF)	10	2756	584	584
Commercial filter (Group CF)	13	2918	378	124
Dacron filter (Group SF)	9	2877	475	14

Arterial blood pH, pCO_2 and pO_2 were determined using an IL combination pH meter.

Thirty minutes after completion of exchange transfusion, each experiment was concluded, and the animal was sacrificed. Positions of catheter tips in the PA and RA were then verified. Portions of the lungs of each animal were fixed in formalin solution and prepared for microscopic exam.

Results

Mean SFP of the blood transfused was elevated prior to filtration (Table 1). SFP decrease after passage through the Dacron filter in Group SF was greater than after passage through the commercial filter in Group CF. In Group NF no filter was used so that preinfusion SFP did not change.

Average platelet and white blood cell counts of the freshly drawn blood were 138,775 ± 15,120/mm^3 and 8102 ± 1604/mm^3 respectively. After five days of storage average platelet and white blood cell counts had decreased to 63,300 ± 32,700 and 4,400 ± 2,605 respectively.

Thirty minutes after completion of transfusion mean systemic arterial blood pressure had fallen in all three groups but was of statistical significance only in the CF group ($p < 0.02$) (Table 2).

Slight increases in average RA pressure in all groups were not of statistical significance (Fig. 1).

The preinfusion mean PA pressure was 16 mm Hg in Group SF, 17 mm Hg in Group CF, and 17 mm Hg in Group NF (Fig. 1). After exchange transfusion mean PA pressure in Group SF was essentially unchanged (15 mm Hg). Average PA pressures rose significantly in Group CF to 24 mm Hg ($p < 0.01$) and in Group NF to 32 mm Hg ($p < 0.005$).

TABLE 2. *Arterial Blood Pressures Before and After Exchange Transfusion*

Group	Pre-infusion (mm Hg)	Post-infusion (mm Hg)
NF	141 ± 45.3	134 ± 34.2
CF	154 ± 24.1	128 ± 13.3
SF	160 ± 32.9	145 ± 19.2

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[*] Extracorporeal Medical Specialities, Inc, King of Prussia, Pennsylvania 19406.

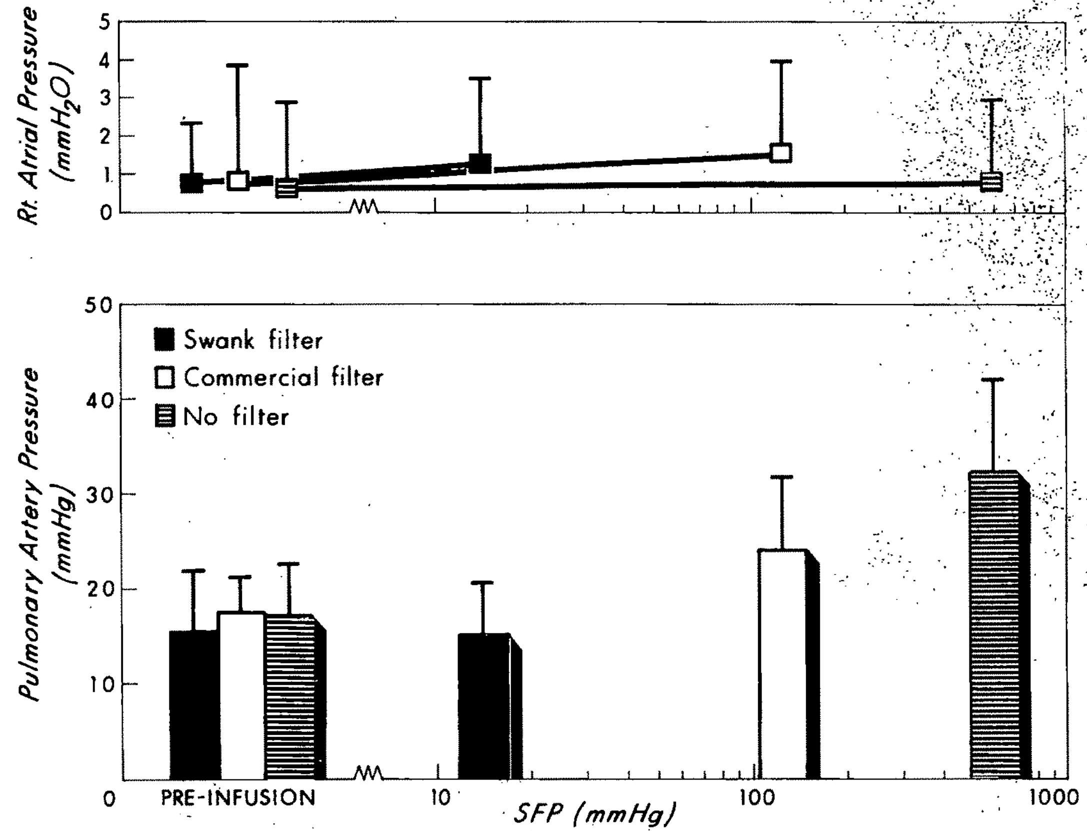

FIG. 1. Pulmonary artery and right atrial pressure changes after exchange transfusions. When either standard commerical blood transfusion filters with 170 μ pores or no transfusion filters were used, pulmonary artery hypertension developed. This did not occur when Dacron wool (Swank) blood transfusion filters were used. Changes in right atrial pressures were not of statistical significance.

In Group SF average arterial blood pO_2 increased slightly from 101 mm Hg before transfusion to 103 mm Hg after transfusion (Fig. 2). In Group CF average arterial pO_2 decreased from 104 mm Hg to 95 mm Hg and in Group NF average arterial pO_2 decreased from 96 mm Hg to 68 mm Hg ($p < 0.02$). There were significant statistical differences between the post-transfusion pO_2 in Group CF and that in Group NF ($p < 0.05$) and between the post-transfusion pO_2 in Group SF and that in Group NF ($p < 0.01$). The difference between the post-transfusion pO_2 in Group SF and that in Group CF was not significant.

In Group SF average O_2 consumption decreased after transfusion to 95% of normal (76 ml/min to 68 ml/min); this change was not of statistical significance (Fig. 2). In Group CF, O_2 consumption decreased to 80% of normal (66 ml/min to 52 ml/min) ($p < 0.001$), and in Group NF average O_2 consumption decreased to 73% of normal (74 ml/min to 55 ml/min) ($p < 0.001$).

Preinfusion average arterial pCO_2 did not differ significantly in the three groups (Fig. 3). A slight fall in pCO_2 in Group SF (31 mm Hg to 27 mm Hg) and a moderate increase in pCO_2 in Group NF (28 mm Hg to 35 mm Hg) were not statistically significant. Essentially no change occurred in Group CF (29 mm Hg to 30 mm Hg).

After exchange transfusion, average arterial blood pH in Group SF decreased from 7.45 to 7.39 ($p < 0.05$). In Group CF average arterial blood pH decreased from 7.46 to 7.29 ($p < 0.001$), and average arterial pH in Group NF decreased from 7.40 to 7.20 ($p < 0.001$). The difference between average post-transfusion pH in Group CF and Group NF was of borderline statistical significance ($p < 0.05$); however the differences between the post-transfusion pH in Group SF and those in Groups CF ($p < 0.01$) NF ($p < 0.001$) were highly significant.

Pathology

On routine microscopic examination using hematoxylin and eosin stains, the small vessels of the lungs of 3 of the 7 animals in Group CF and all of the animals in Group NF were noted to be filled with "cellular stroma." In none of the animals in Group SF was such changes noted.

Discussion

It has been postulated that pulmonary microembolism associated with blood transfusion is a cause for post-traumatic pulmonary insufficiency.[4,6,7,18,21,26,27] If this does occur then one would expect that massive transfusion with blood containing microaggregates would also be associated with pulmonary hypertension.[2,3,14,16,27] In the present experiments SFP of the blood before transfusion was markedly elevated indicating that it contained great numbers of microaggregates. When this blood was transfused and no filters were used or if standard commercial transfusion filters were used, considerable mechanical obstruction of the

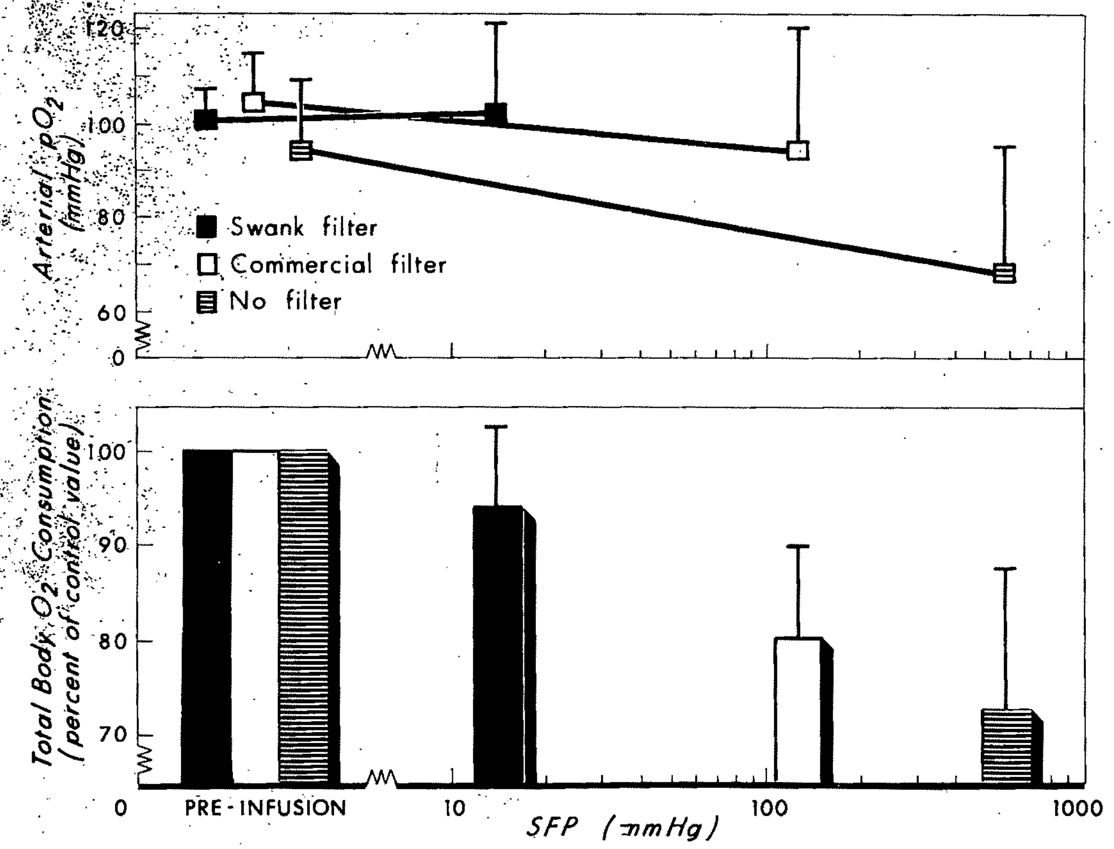

FIG. 2. Oxygen consumption and arterial oxygen tension changes after exchange transfusion. When transfusion filters were not used, total body oxygen consumption and arterial oxygen tension decreased markedly. Use of standard commercial blood filters was also associated with a decrease in oxygen consumption, but oxygen tension changes were less. When Dacron wool (Swank) blood transfusion filters were used, O_2 consumption changes were only slight and O_2 tension decreases were completely prevented.

pulmonary vasculature probably occurred. This was evidenced by marked elevations in PA pressures and further confirmed by pathologic examinations which revealed the presence of microaggregates in the small blood vessels of the lungs. These changes were prevented when the blood transfusions were passed through Swank Dacron-wool blood transfusion filters.

Mechanical obstruction due to embolization may not have been the only cause for the observed increase in PA pressure. The homologous blood syndrome has been noted in both animals and patients after blood transfusion and its effects closely resemble those noted in Groups NF and CF in these experiments.[5,10,11] Such changes did not occur, however, when transfusions were passed through Swank Dacron wool blood transfusion filters and micro-aggregates were removed. Thus it may well be that the changes associated with the homologous blood syndrome may be caused at least in part by microaggregates removed by dacron wool filtration but not by standard blood transfusion filtration.

Dow *et al.*[10] found that factors causing the homologous blood syndrome in dogs are localized in the plasma. Since platelets remain in the plasma after packed red cells are separated, those data would tend to further verify this hypothesis.

Serotonin, large amounts of which is contained in platelets, also causes pulmonary vascular constriction and its effects are not dose related (15). In these experiments filtration of four units of blood through a single Swank filter lead to a decrease in blood serotonin concentration from 0.029 mcg/ml to 0.011 mcg/ml, a decrease of 62%. Other vasoactive substances and the decreased arterial pH may also have been additive.[12,17,29]

Exchange transfusion without blood filters or through standard blood transfusion filters with 170 micron pores caused not only pulmonary hypertension but also a decrease in total body O_2 consumption. Again this change did not occur when Swank Dacron wool blood transfusion filters were inserted into the transfusion line.

Microaggregates are composed principally of platelets, old white blood cells, and fibrin, and their accumulation in the stored blood used in this research was associated with a drop in free platelet and white blood cell counts during storage. Removal of large amounts of these PWF aggregates must certainly have accounted, at least in part, for the lack of changes in O_2 consumption of animals transfused through the Swank Dacron wool filters.

The average pH of the transfused blood was 7.02 ± 0.10. This was undoubtedly lower than the arterial blood pH of the animals receiving the transfusions, and must have contributed to the metabolic acidosis noted in all experiments. Since the marked decrease in arterial blood pH was less in

Group SF than in Groups CF and NF, it appears unlikely that the low pH of the transfused blood was the only etiologic mechanism. Even though excess lactate was not determined the more severe metabolic acidosis noted in Groups CF and NF was probably due in part to the decreased O_2 consumption and tissue hypoxia.

The data further suggest that pulmonary vascular obstruction may have caused a reduction in cardiac output and that there was possibly a marked increase in peripheral vascular resistance. If such changes did occur, they might also have contributed to development of a metabolic acidosis. Venous O_2 content and cardiac output determinations would have allowed verification of this hypothesis, but regrettably such measurements were not performed in these studies.

Tobey *et al.*[36] were unable to demonstrate arterial O_2 tension changes in shocked baboons resuscitated with stored blood having an elevated SFP. Neither were such changes demonstrated in the present research; change in O_2 utilization were seen in this research only because O_2 consumptions were followed.

Marshall *et al.*[20] did not observe significant changes in pulmonary function after massive transfusion with ACD preserved blood of otherwise healthy dogs; however SFP of the canine blood used in their experiments was not elevated, thus indicating the absence of microaggregates larger than 20μ.

In other research currently in progress in these laboratories, however, when blood with a markedly elevated SFP was transfused to dogs through a standard transfusion filter, the same changes as herein reported occurred. Anatomical shunting of blood through the lungs (Qs/Qt) increased from a preinfusion value of 10% to a post-infusion value of 23%, and pulmonary diffusing capacity (DO_2) decreased from 5.6 to 3.0. Ventilation-perfusion ratio (VA/Qc) showed no change from preinfusion values. No change in degree of shunting occurred when the blood was transfused through Swank filters. These data, which will be reported subsequently, further confirm and clarify those presently reported.

The changes noted in Group NF experiments in which the blood was not filtered certainly may represent gross pulmonary embolization, and this may account for the increased severity of changes noted in these animals when compared to those in Group CF in which standard transfusion filters were used. Such appears doubtful, however, since in Group CF the inline transfusion filters would not only have prevented infusion of gross blood clots but would also have removed large PWF aggregates. Additionally, blood clots were noted in none of the transfusions whether or not blood filters were used.

Standard blood transfusion filters in general use today consist only of a screen clot filter with 170 μ pores, and they transmit particles smaller than that size. Since physiologic changes did not occur in the present experiments when animals were infused through Dacron wool filters, it appears

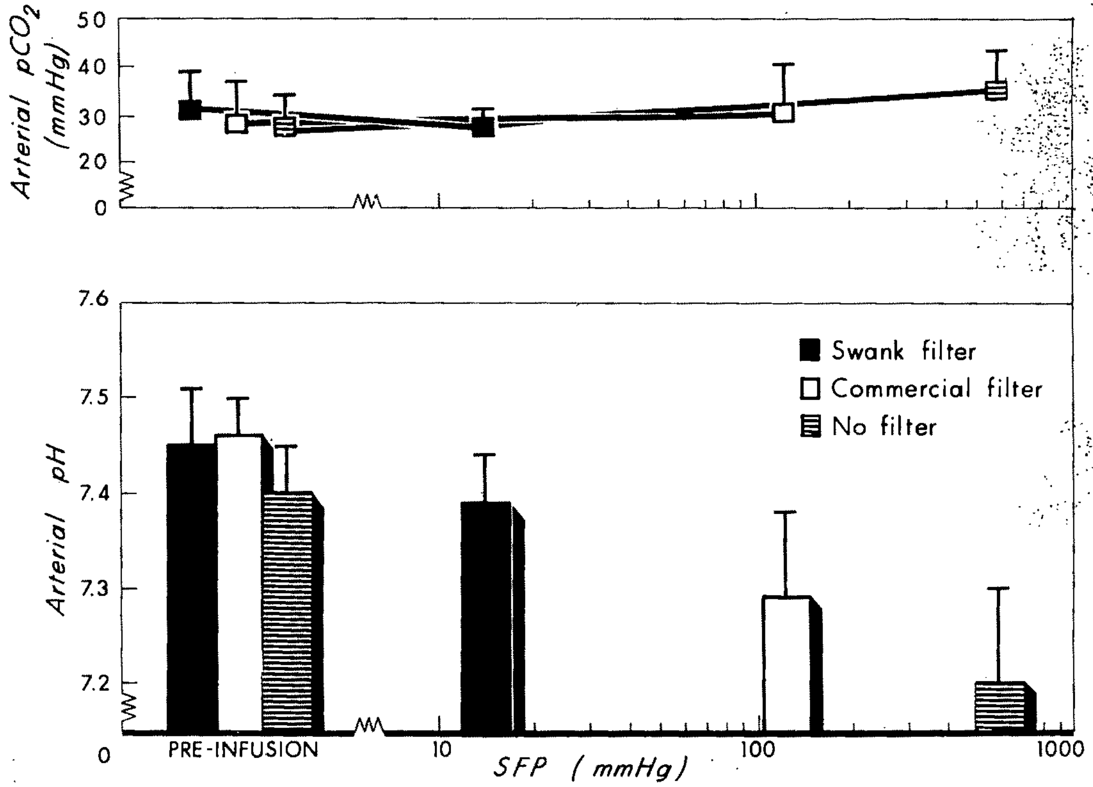

FIG. 3. Arterial blood pH and carbon dioxide tension changes after exchange transfusions. When either commercial blood transfusion filters with 170 μ pores or no transfusion filters were used, metabolic acidosis developed. This was not nearly as severe when Dacron wool (Swank) blood transfusion filters were used. Arterial carbon dioxide tension did not change significantly.

likely that the changes produced by exchange transfusion through the standard commercial blood transfusion filters were caused by microaggregates ranging in size from 15 μ to 170 μ in diameter.

Transfusion of unfiltered blood containing large numbers of PWF microaggregates should lead to pulmonary microembolism and its consequent physiologic changes. However it has not previously been demonstrated *in vivo* that standard commercially available blood transfusion filters are only partially protective against such microemboli. Furthermore, the almost complete prevention in these experiments of the detrimental effects of transfusion of blood with an increased SFP through Swank Dacron wool blood transfusion filters was striking.

Microaggregates in stored human blood and those formed in the canine blood in this research seem to respond in similar fashion.[7,8,30,33] However the ultimate fate of these transfused microaggregates has not yet been clarified.[32,33] It is possible that after lodging in the pulmonary capillaries, they may break down and release lytic enzymes from their organelles capable of damaging surrounding tissue. Microemboli may also migrate through the pulmonary capillary bed into the arterial circulation. Embolization to other capillary beds may then occur and widespread destruction of other body tissues result.

The Swank Dacron wool blood transfusion filter is an outgrowth of extensive research begun in 1961.[31] Initially, use of this filter was confined to filtration of blood in pump oxygenator operation. Because of its dramatic success in preventing harmful sequelae associated with extracorporeal circulation, a smaller filter for use in blood transfusion has recently been prepared. The blood transfusion filter consists of a nylon screen clot filter followed in sequence by a Dacron wool mesh (Fig. 4). Its filtration characteristics utilizing human blood, have been described in detail elsewhere.[19,30]

Essentially, the Swank blood transfusion filter removes aggregates and amorphous debris down to a size of approximately 15 μ in diameter. The same quantities of nonaggregated platelets and white blood cells are removed by passage through either standard blood transfusion filters or Swank Dacron wool filters.[19] However standard blood transfusion filters pass microaggregates in such large numbers that blood SFP remains elevated. A single Swank transfusion filter effectively removes such microaggregates from up to four units of stored human blood.[19]

It appears to these authors that this research is of great clinical significance. It has been assumed for sometime that transfusion of blood containing microaggregates is a cause for post-traumatic pulmonary insufficiency. However because canine blood stored in ACD solution does not develop an increased SFP, it has been difficult to establish a model so that this phenomenon might be demonstrated *in vivo*. In addition the physiologic effects of PWF microaggregates filtered through standard blood transfusion filters have not been clearly defined in vivo. The experimental model herein represented by Group CF appears analogous to the clinical situation in which a patient is transfused through a standard blood transfusion filter with a large amount of stored blood in which great numbers of microaggregates have accumulated. Were this to occur then one might well expect to see the same sorts of changes as

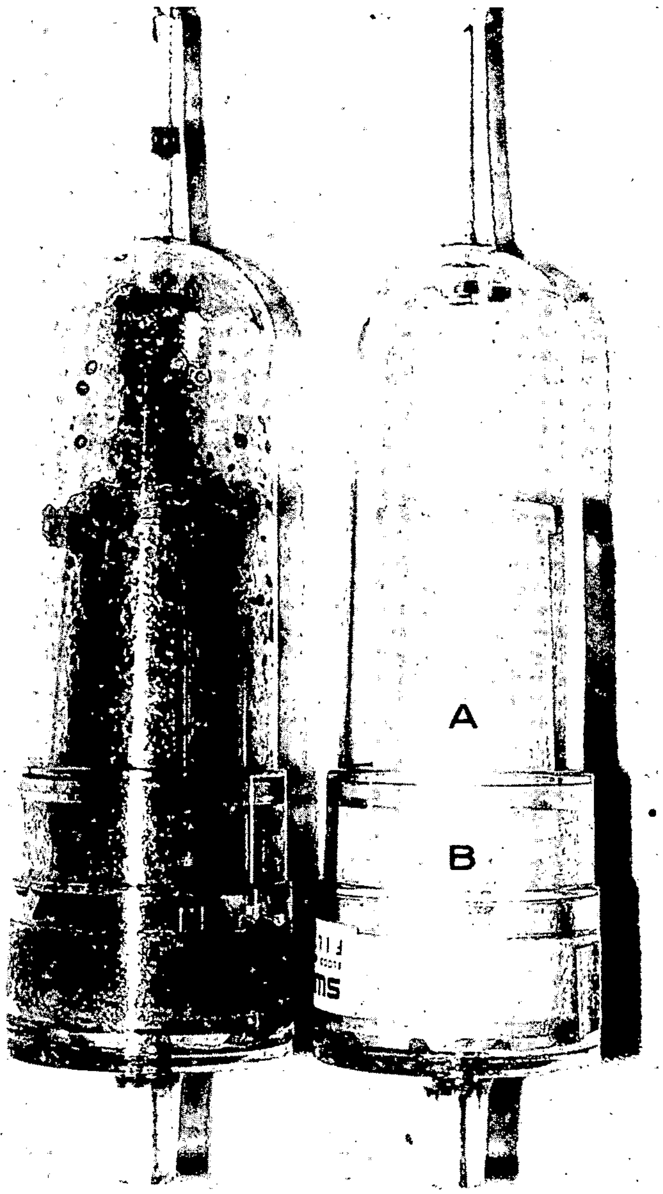

FIG. 4. (Right) Swank Dacron wool blood transfusion filter. Spike at upper end is inserted into blood transfusion container and standard intravenous set is inserted into lower part of the filter. Blood then passes through nylon screen clot filter (A) and Dacron wool mesh (B). Particles passing this filter are 15μ in diameter or smaller and up to 2000 cc of 21-day-old human whole blood may be filtered under pressure before larger particles are forced through.[19] (Left) Appearance of a Dacron wool (Swank) filter from a typical experiment. Larger aggregates are filtered out by the upper nylon screen clot filter while those passing the clot filter are removed by the lower dacron wool mesh.

were noted, i.e. pulmonary hypertension, decreased O_2 consumption and metabolic acidosis.[27] If such is to be prevented in patients, then massive transfusion with stored blood should only be administered through appropriate micropore blood transfusion filters. This research indicates that Swank Dacron wool blood transfusion filters are highly effective in removal of harmful microaggregates from such blood.

It may well be that all blood transfusions should be administered through Swank Dacron wool filters. When only one or two units of blood are to be administered, the lungs may be able to adequately compensate for the physiologic insult from relatively minor quantities of pulmonary microemboli. However there would appear to be no reason to add this burden to the lungs of an already severely injured or ill patient unless absolutely necessary. The removal of microaggregates from all blood transfusions should, therefore, be highly desirable. This research has clearly demonstrated that removal of such particles can be accomplished by using Swank Dacron wool blood transfusion filters, but not by using standard commercially available blood transfusion filters in general use today.

Acknowledgment

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Stability of Normal Human Fecal Flora During a Chemically Defined, Low Residue Liquid Diet

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Ten adult male volunteers (medical students) subsisted for seven days upon a chemically defined, low residue liquid diet, and consumed 1200–1800 calories per day. All stools were collected; three were cultured within the hour—a prediet stool, one collected on the seventh day, and a postdiet stool. Specimens were diluted anaerobically, and anaerobic cultures were streaked upon plates of prereduced agar media and incubated in Brewer jars. During the low residue diet, total fecal mass was relatively small and each subject passed only two or three stools. The mean reduction in daily fecal output was 70%. Mean counts of total aerobes were 10^7/gm throughout the study, and mean counts of total anaerobes were 10^{10}/gm. There was no overgrowth by opportunistic bacteria or fungi. The low residue food did not alter fecal flora; there was neither disappearance nor reduction of any bacterial group.

CHEMICALLY DEFINED, low residue diets may be used clinically to provide complete nutritional maintenance of patients in need of a liquid dietary regimen of high nutritional value.[5] Defined diets offer nutritional support in gastrointestinal disorders such as chronic inflammatory bowel disease, short bowel syndrome following substantial resection of the small intestine and malabsorption syndromes. Elemental diets may also be used preoperatively to provide nutrition to patients scheduled for colonic surgery, postoperatively after gastrointestinal surgery when low residue foods are desirable, and in the management of problems of mastication and fecal incontinence.

Employing chemically defined diets as the sole source of nutrition, Winitz and colleagues[7] found that the weight of volunteers remained stable and noted no biochemical abnormalities. They also reported[6] a 70–80% decrease in stool excretion and a decrease in the concentration and types of fecal bacteria. Both Attebery[1] and Glotzer[3] and their colleagues have confirmed the reduction of fecal volume during elemental, low residue diets, but have not demonstrated a decrease in the concentration and types of fecal bacteria. We have employed a similar defined low residue diet, and have assayed its effect upon the fecal flora of normal adults.

Methods

Ten healthy male medical students ranging in age from 23 to 31 years (mean age ± standard deviation = 25.9 ± 3.0 years) participated in this study. Each maintained himself on a chemically defined, low residue diet (W-T Low Residue Food®) for seven days. Four to six 300 calorie packets (320–480 gm) furnished dextrin as the carbohydrate, crystalline L-amino acids, vitamins, minerals and a source of essential fat, but lacked protein, starch, indigestible material and additional bulk. Each subject was allowed water *ad libitum* while on the low residue diet. No other foods were allowed.

Three stools from each subject were cultured for quantitation and identification of microflora. The first stool was collected the day before the subject began the defined diet, the second was taken on the seventh day of the defined diet, and the third was obtained three days after resumption of the subject's regular diet. In addition, all stools passed were collected, weighed, and examined for color, odor and consistency. A weighed sample of each was dried overnight in a vacuum oven at 60 C in tared pans so that the dry weight could be obtained and the percentage solids calculated.

The subjects received no medication in the week prior to, or during the diet period. Each took one 5 mg bisacodyl NF tablet (Dulcolax®) on the evening before starting the defined diet to facilitate cleaning the bowel of residue remaining from the normal diet, and with the first feeding of the de-

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fined died, two 10 grain refined charcoal tablets as a marker for gross and microscopic observation. Intestinal transit time during a chemically defined, low residue diet has been estimated at five to seven days.[1]

All stools were collected in 11.5 × 13 inch plastic bags. Those to be cultured were processed within 30 minutes of excretion. Each was kneaded in the plastic collection bag to provide a homogeneous specimen; a 0.1 gm sample was transferred to a tared screw cap tube and emulsified in 9.9 ml fluid thioglycollate medium with the aid of a vortex mixer. Serial 100-fold dilutions were then continued under a stream of O_2-free CO_2 in prereduced fluid thioglycollate medium in rubber stoppered tubes. All dilutions were plated aerobically employing blood agar medium (5% human blood in brain-heart infusion agar containing 4% agar), MacConkey agar, mannitol salt agar, cornmeal agar, and Sabouraud agar. These plates were examined after 24 and 48 hours, except cornmeal agar and Sabouraud agar which were inspected after 10 days.

For anaerobic culture, plates of blood agar medium and Rogosa SL agar were prereduced by storage for at least 48 hours in a flexible plastic anaerobic glove box containing an environment of 5% CO_2, 10% H_2, and 85% N_2. Reduced plates were removed from the glove box in sealed Gas-Pak® jars so that they would be exposed to room air only during inoculation. The inoculum was spread on the agar surface, and anaerobic plates were immediately incubated in Brewer jars. These were evacuated and filled with a mixture of 95% H_2 and 5% CO_2 three times before being clamped off. In the interim, plates in partially filled Brewer jars were kept under a stream of O_2-free CO_2 until the jar could be sealed, evacuated, and gassed. All anaerobic plates were incubated for at least four days before being examined and subcultured. All media were incubated at 37 C, except for cornmeal agar and Sabouraud agar at room temperature.

Reduced brain-heart infusion agar roll streak tubes were inoculated from each specimen under a stream of O_2-free CO_2, but did not yield total counts of anaerobes different from those obtained from plate cultures. In addition, tubes of brain-heart infusion broth, fluid thioglycollate medium, and cooked meat medium were inoculated from the initial dilution of each specimen. These allowed both aerobic and anaerobic bacteria to grow, and were studied as a check on the organisms isolated from surface cultures. The growth of species on appropriate selective media also served as an internal check. Aerobic isolates were streaked to eosin-methylene blue agar to identify coliforms, and were subcultured to heart infusion broth, from which Gram-stained smears were prepared. Standard methods were used to identify Gram-negative enteric bacteria. Isolates from anaerobic plates were streaked to a blood agar plate for aerobic incubation to verify that the isolate was an anaerobe.

All bacterial counts were transformed to logarithms to the base 10 for ease of statistical analysis. Mean differences between treatments were examined by the *t* test. The criterion for random distribution between two treatment groups was selected as a probability (P) equal to or greater than 0.05 with 18 degrees of freedom ($t < 2.101$).

Results

Each subject passed only two or three stools during the seven days of the defined diet. Table 1 indicates that the mean daily output of feces was diminished 70% during this period. This difference was statistically significant ($P < 0.001$). The mean daily output after resumption of a regular diet by each subject was not significantly different from output initially. This table also shows that the mean percentage of fecal solids was not altered significantly during the period of the defined diet. Although the mean body weight of subjects decreased three pounds during the diet and increased subsequently, these changes are not significantly different, and represent intestinal bulk lost during the low residue diet period and regained subsequently.

Observation of stools for color, odor and consistency indicated that these properties generally remained unchanged. However, three subjects, who passed liquid stool on the sixth and seventh day of the defined diet, experienced neither pain, discomfort nor cramping. The initial and sometimes the second stool of the diet period was noted to be darker or to have dark patches due to the charcoal used as a marker. This was confirmed by microscopic examination.

Quantitative bacteriological studies indicated that the change to the chemically defined, low residue diet caused no alteration of fecal flora. Table 2 summarizes the means for total aerobes and anaerobes, and for the several groups of aerobic and anaerobic bacteria. Although mean values for some bacterial groups were lower during the defined diet, none of the differences between pre-diet and diet means and pre-diet and post-diet means was statistically significant. Bacteroides were the predominant microorganisms in feces, and were followed in descending order of concentration by lactose-fermentating coliforms (*Escherichia* and *Enterobacter*), the fusobacteria, anaerobic lactobacilli (*Bifidobacterium*), other anaerobic Gram-positive rods, and streptococci. The clostridia, veillonellae, and peptostreptococci were minor anaerobic constituents, and staphylo-

TABLE 1. *Influence of a Chemically Defined, Low Residue Liquid Diet on 10 Healthy Adult Males*

	Mean ± Standard Deviation		
	Pre-diet	Diet	Post-diet
Feces produced, grams wet weight per day	157.5 ± 70.1	43.4 ± 17.6	126.5 ± 55.7
Percentage dry fecal solids	26.3 ± 7.5	25.7 ± 6.7	28.0 ± 9.1
Body weight, lbs.	188 ± 27	185 ± 25	191 ± 22

TABLE 2. *Bacterial Counts of Feces* from 10 Healthy Adult Males*

Microorganism	Pre-diet	Diet	Post-diet
Total aerobes	7.82 ± 0.79	7.67 ± 1.12	7.46 ± 1.32
Total anaerobes	10.41 ± 0.23	10.52 ± 0.33	10.30 ± 0.87
Escherichia	7.56 ± 0.74	7.09 ± 1.52	6.97 ± 1.28
Enterobacter	3.65 ± 2.77	1.28 ± 2.47	2.29 ± 2.67
Streptococcus	4.02 ± 2.90	3.19 ± 2.69	6.08 ± 2.22
Staphylococcus	1.36 ± 2.37	2.22 ± 2.28	1.22 ± 2.00
Lactobacillus	2.81 ± 3.71	1.99 ± 3.35	2.76 ± 3.75
Bacteroides	10.11 ± 0.39	10.39 ± 0.38	10.09 ± 0.90
Fusobacterium	6.91 ± 4.77	6.92 ± 4.56	7.45 ± 4.04
Veillonella	1.25 ± 2.93	1.94 ± 3.85	3.08 ± 4.52
Clostridium	2.74 ± 3.25	1.53 ± 2.38	1.43 ± 3.17
Bifidobacterium	6.92 ± 3.82	6.14 ± 3.36	6.40 ± 4.22
Other anaerobic Gram-positive rods	6.58 ± 4.56	4.73 ± 4.62	2.90 ± 4.48
Peptostreptococcus	1.03 ± 2.92	1.82 ± 3.83	1.12 ± 3.21

* Arithmetic means of $\log_{10}$/gram wet weight ± standard deviation.

cocci and lactobacilli were minor aerobic constituents of the flora. Fungi were not found, and yeasts were isolated only from the diet stool of two subjects (log values of 4.42 and 5.90). There was no overgrowth of opportunistic bacteria or fungi with use of the defined diet. Bacteroides were isolated easily without use of selective media containing antibiotics. Aerobic and anaerobic blood agar plates served as the primary medium for colony counts with the other selective media employed only as a supplementary back-up.

Discussion

The defined low residue diet diminished stool mass and decreased the frequency of stool passage. Concomitantly, there was no marked reduction in bacterial population nor was there disappearance or reduction of particular bacterial groups. In this regard, our findings confirm those of Attebery *et al.*[1] and Glotzer *et al.*[4], but not those of Winitz *et al.*[6] The present study utilized specimens of fresh feces obtained under ideal conditions from ten healthy adults receiving no medication as opposed to specimens obtained from hospitalized patients. This report establishes baseline data of value for future studies of changes in human fecal flora.

Our previous report[2] and that of Nichols and colleagues[4] regarding the effect of preoperative mechanical preparation of the colon by means of enemas, cathartics, and low residue or clear liquid diet have shown reduction in the total fecal mass and either no change in the concentration of any fecal microorganism or reduction in the concentration of coliforms, respectively. Although fecal output was diminished 70% as a result of the low residue diet, it may be calculated from the results of the present study that the total bacterial content of the fecal mass was only lowered from 4.07×10^{12} to 1.44×10^{12}. Thus, any feces remaining in the colon contain such large numbers of bacteria that their potential for infection remains a major hazard following colonic operations. Accordingly, use of defined diet alone would be inadequate for intestinal antisepsis for preoperative preparation of the colon, and should be accompanied by the additional administration of appropriate oral, nonabsorbable antibiotic(s) in the regimen.

Acknowledgments

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Pyeloureterostomy Reconstruction in Human Renal Transplantation

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Pyelouretersotomy or ureteroureterostomy was the urinary tract reconstructive procedure in 114 of 132 consecutive renal transplants performed at the Massachusetts General Hospital from September 1967 to December 1973. Anastomotic leakage was the only complication related to failure of pyeloureterostomy or ureteroureterostomy. This occurred in nine transplants (7.9%). Since 1970, only four anastomotic leaks have occurred in 79 consecutive pyeloureterostomies or ureteroureterostomies. Six of the nine primary anastomotic leaks were corrected either by retrograde ureteral catheter drainage or re-suturing of the anastomotic defect. Only one patient died as a result of complications following a leak. The operative technique is described with emphasis on the important details believed necessary for consistent success in performing this procedure.

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THE CONTINUING IMPORTANCE of technical complications in human renal transplantation is emphasized by the most recent report of the Human Renal Transplant Registry.[8] In this report, which included 12,389 transplants, 12% of the kidneys were lost primarily because of technical problems. Review of the literature indicates that the majority of technical failures and complications are related to the urological reconstruction.[1-3,7,9,13-15,17]

Most authors now recommend the ureterovesical anastomosis as the reconstruction procedure of choice.[1-3,7,9,13,14] This consensus has resulted from the reported 14–50% incidence of anastomotic leakage with pyeloureterostomy and ureteroureterostomy and the subsequent failure of salvage procedures.[7,9,13,15]

Nevertheless, there are practical and theoretical disadvantages to the ureterovesical reconstruction technique and a review of reported series indicates a significant incidence of immediate and late post-transplant complications. Leakage from the ureteral implant site and the bladder closure varies from 2–21%.[1,3,4,13,14] Late post-transplant ureteral obstruction is reported in 2–7% of cases. Ureteral necrosis resulting from either failure to preserve adequate blood supply during donor nephrectomy or from rejection is a complication seen in every large series.[1,3,4,7,13-15] The necessity of a bladder catheter for four to seven days to protect the bladder closure and implant is a significant consideration in the immunosuppressed patient and Starzl has reported a slightly greater incidence of urinary tract infections with the ureterovesical technique.[17] Excessive bleeding from the bladder incision necessitating frequent irrigation or catheter replacement to remove obstructing blood clots is not an infrequent problem and has resulted in disruption of the ureteral anastomosis.[2,9] The necessary dissection around and opening of the bladder, difficulty in immediate postoperative retrograde catheterization and increased possibility of reflux, are disadvantages that could lead to major complications.

Advantages of the ureteroneocystostomy include fewer early anastomotic failures: probably related to the more meticulous technique and experience necessary in performing the pyeloureterostomy. The former approach also retains the possibility of conversion to a pyeloureterostomy if the implant fails.

Pyeloureterostomy and ureteroureterostomy reconstructions have been criticized primarily because of the previously mentioned incidence of early anastomotic leaks. Other objections are the infrequent late obstructions following ureteroureterostomy,[17] the necessary urinary tract evaluation pre-transplant, and the necessity of ipsilateral

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nephrectomy. In past descriptions of this technique, protective nephrostomy and ureteral stents were recommended, but most authors, including ourselves, now feel that this is not necessary and probably leads to significant morbidity.[7,10]

The advantages of the pyeloureterostomy or ureteroureterostomy include almost complete avoidance of early and late obstruction, ureteral slough, and prolonged bladder catheterization. In 1966, Leadbetter *et al.* described the technique for pyeloureterostomy and ureteroureterostomy used in transplant urinary tract reconstruction at our institution. This technique was used in 25 transplants, from 1963 to 1966. One leak was encountered from failure of the anastomosis.[10] Since September, 1967, 114 pyeloureterostomies or ureteroureterostomies and 18 ureterovesical implants have been performed during 132 consecutive renal allotransplants at the Massachusetts General Hospital. There were 40 living-related and 92 cadaver donors. These procedures were all performed by or under the direct supervision of the authors.

It is the objective of this report to review the results of urological reconstruction using pyeloureterostomy or ureteroureterostomy as compared to the ureterovesical implantation in our own series and in those of others. In this report, ureteroureterostomies will be classified with pyeloureterostomies, since the exact location of the anastomosis is sometimes difficult to determine. The operative technique used in pyeloureterostomy will be described in detail. Adherence to meticulous technique may explain the relative freedom from complications in this series as compared to other reported experiences.

Methods

The technique of pyeloureterostomy used in this program is similar to that previously described by Leadbetter *et al.*[10] Minor technical modifications have been made to avoid complications that occurred in the earlier years of our experience.

Special care is taken to leave the recipient ureter sufficiently long to avoid tension at the anastomosis. Excessive redundancy of the recipient ureter is also avoided as this may lead to kinking of the ureter and obstruction. Before constructing the anastomosis, the thin connective tissue over the anterior surface of the recipient ureter is divided thus removing potentially obstructive bands. Occasionally, this division has extended several centimeters distally when it appeared that the ureter might become kinked against these bands.

Six-O chromic suture is utilized in place of 5-0. The smaller swedged-on suture avoids the larger holes left by the 5-0 chromic in the thin ureteral and pelvic walls, from which we have observed significant urine leakage. Recently, we have also used 7-0 Tevdek with no apparent problems to date. The use of a small, non-absorbable suture of greater tensile strength than 6-0 chromic has obvious advantages, but a greater period of follow-up is needed to determine any disadvantages.

If pyeloureterostomy is to be considered, the ipsilateral kidney is removed through the transplant incision. To accomplish this, it is usually necessary to extend the lateral edge of the incision several centimeters for adequate exposure. The kidney is exposed by continuing the retroperitoneal dissection cephalad. The kidney is mobilized except for the hilar area. It is then retracted caudally, and the renal vessels are exposed, ligated, and divided. The ureter is divided near the ureteropelvic junction. Occasionally, it is necessary to divide the ureter prior to exposure of the hilar area. Polycystic kidneys are usually removed at a prior operation, since their size frequently makes removal difficult and hazardous through this route. Following revascularization of the graft, the distal recipient ureter is identified and dissected from its retroperitoneal position, with care being taken to preserve its blood supply. Several nutrient vessels may be seen traversing the ureteral "mesentery" and in most cases, these vessels can be preserved. The ureteral dissection is continued until an adequate length is obtained to reach the donor pelvis without creating tension on the anastomosis. The ureter is inspected for caliber, patency and vascular supply. If any abnormalities are present, pyeloureterostomy is not performed. If the recipient ureter is satisfactory, the donor hilar area is inspected to rule out the presence of a bifid pelvis. The presence of a double collecting system requires modification of the technique.[3]

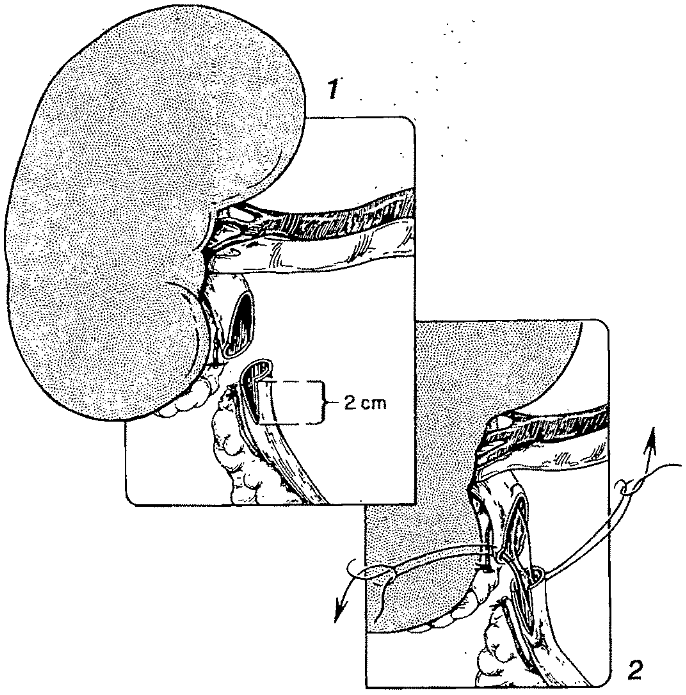

FIG. 1. Spatulation of the donor pelvis and recipient ureter. FIG. 2. Placement of the matress sutures at the apices of the anastomosis.

In final preparation for the pyeloureterostomy, the donor ureter is opened along its anterior medial surface to a point where the diameter of the lumen increases near the ureteropelvic junction. If the pelvis or ureteropelvic junction is intrarenal, dissection of the hilar area is avoided and a ureteroureteral anastomosis is performed.

When the position of the distal apex of the anastomosis is determined, the donor ureter is divided at that point. The donor ureter is opened approximately 2 cm along the anterior medial surface to the proximal apex of the anastomosis which is usually within the renal pelvis (Fig. 1).

The length of recipient ureter necessary to reach the proximal apex of the anastomosis without tension is determined and the recipient ureter is divided at that point. The ureter is opened along its posterior lateral surface for approximately 2 cm to the distal anastomotic apex (Fig. 1). Care is taken to avoid the major vessels on the posterior surface of both the donor and recipient ureters.

Everting mattress sutures are placed at each apex to secure a tight closure at these points (Fig. 2). The apices are then rotated 180° exposing the back wall (Fig. 3). Stay sutures are not used. The back wall anastomosis is performed first as this is the most difficult. The first two sutures at the distal apex are placed with great care, as improper placement results in leaks at this point and poor alignment making the remainder of the anastomosis difficult. The sutures are placed approximately 0.5 mm apart and about the same distance from the anastomotic edges. The sutures are carried to the opposite apex and tied (Fig. 4). Once placed, the needle is not withdrawn unless the next needle pass is behind the unoccupied hole from which continual leakage will otherwise frequently occur. If a leak is present at the completion of the anastomosis, it should be closed by sutures placed at the same depth as those of the suture line. A deeper suture appears to apply greater stress on the tissue producing a pinpoint leak through the suture track.

One or two penrose drains placed in the operative wound are removed when the wound drainage is minimal, usually within 48 hours.

Foley catheter drainage of the bladder is maintained during the immediate postoperative period until diuresis has slowed and replacement fluid requirements have stablized.

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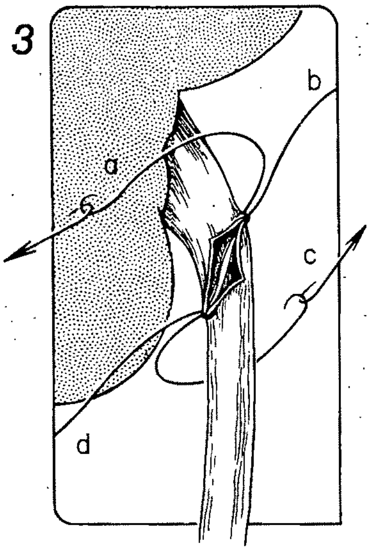

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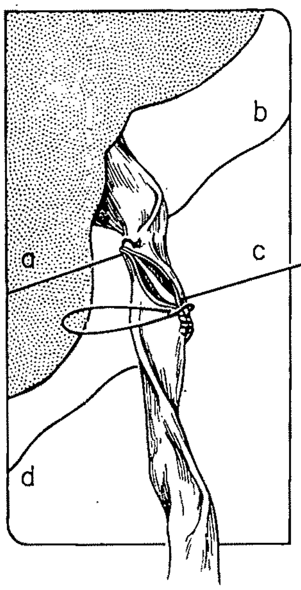

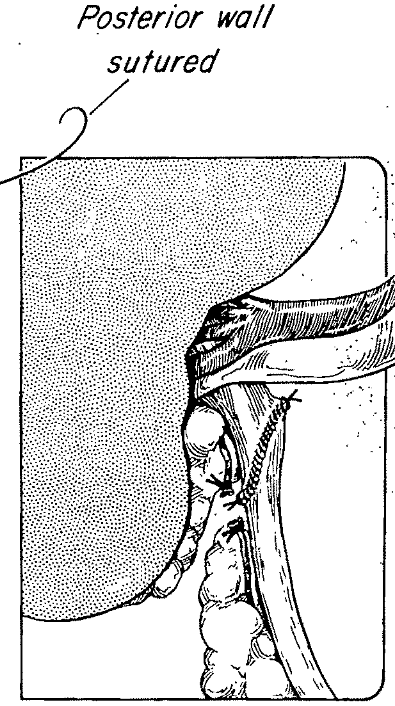

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FIG. 3. Direction of rotation of the pelvis and ureter to expose the back wall of the anastomosis. FIG. 4. Initial suture placement in the back wall of the anastomosis. FIG. 5. Completed pyeloureterostomy.

In our experience, the catheter can usually be removed within the first 24 hrs. postoperatively.

In this series, Imuran* and prednisone were the primary immunosuppressive agents. Prior to 1972, selected patients received antithymocyte globulin (ATG)† intramuscularly. Since 1972, a study has been in progress in which intravenous ATG is being given to patients selected at random in addition to standard immunosuppression.

The ureteroneocystostomy utilized in our bladder implant procedures has been well described by others.[1,6,16]

Post-transplant intravenous pyelogram or retrograde catheterization studies were obtained in the early postoperative period with few exceptions in this series.

Results

Of 114 pyeloureterostomies performed, significant postoperative complications related to the technique occurred in nine instances (7.9%). Table 1 summarizes the pertinent information concerning these nine patients. Technical failure in achieving a tight closure was considered to have caused leakage in six of the nine anastomotic failures. Primary repair of the leak was performed in four of these six technical failures with 1 transplant being lost due to failure of the reconstructive attempt and severe rejection. Two patients developed leakage from apparent anastomotic disruption following re-exploration for wound hemorrhage. Both patients lost their transplants from failure of the reconstructive procedures. In three patients, leakage was satisfactorily controlled with retrograde ureteral catheter drainage and re-suture of the anastomotic defect was not necessary. There was only one late complication directly

TABLE 1. *Anastomotic Leaks Directly Related to Pyeloureterostomy*

No.	Patient	Date of Transplant	Donor	Day of Leak Dx. post-Tx.	Function	Cause of Leak	Treatment	Results
1	P.G.	1968	C	27 days	delayed	Technical failure.	Suture closure of defect over a ureteral stent without nephrostomy.	Good
2	R.B.	1968	C	1 day	immediate	Probably technical failure. Diagnosis made with Indigo carmine blue. Not demonstrated on retrograde study.	Retrograde cath drainage for 14 days.	Good
3	J.P.	1969	C	12 hrs.	immediate	Technical failure.	Primary repair over a ureteral stent following failure of control by ureteral cath. drainage.	Graft removed due to continual leakage & rejection. Pt received 2nd transplant.
4	E.S.	1969	C	1 day	immediate	Technical failure.	Retrograde cath. drainage for 14 days.	Good
5	B.M.	1969	C	2 days	immediate	Technical failure and disruption of the anterior wall of the anastomosis with retrograde cath.	Two attempts at re-suturing over a ureteral stent with nephrostomy drainage.	Good*
6	A.G.	1970	LR	12 hrs.	immediate	Torsion of renal vein resulted in hematuria and an obstructive blood clot in distal ureter.	Removal of obstructing clot and ureteral cath. drainage for 24 hours.	Good
7	P.G.	1971	C	54 days	immediate	Anastomotic disruption following third re-exploration for wound hemorrhage.	Primary repair over ureteral stent with nephrostomy drainage.	Unsuccessful. Pt. died from generalized septicemia and meningitis.
8	M.V.	1973	LR	8 days	immediate	Probable anastomotic disruption following wound exploration and suture of ruptured kidney.	Attempted primary repair after failure of retrograde drainage with ureteral stent and nephrostomy.	Unsuccessful. Graft removed due to severe rejection and wound infec.
9	J.I.	1973	C	24 hours	immediate	Technical failure and high urine output. Leak closed spontaneously in 36 hrs. Pt. returned in 6 wks. with leak into an abcess.	Primary repair over ureteral stent and nephrostomy drainage.	Good†

* Patient died from a ruptured sigmoid diverticulum 6 months post-transplant. Previous complicated hospital course may have contributed to her inability to respond to treatment.

† Patient probably developed a small abscess at the point of initial urine leakage. The abscess appeared to erode the suture line two months post-transplant. IVP five days post-transplant was normal. Surgical repair was successful but two days before planned removal of the nephrostomy tube, the patient committed suicide. He had a long history of depression and previous suicide attempts.

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* Azathioprine, Burroughs Wellcome & Co., Inc., Tuckahoe, N.Y.

† Antithymocyte globulin, The Upjohn Company, Kalamazoo, Michigan.

TABLE 2. *Anastomotic Leaks Directly Related to Ureteroneocystostomy*

No.	Patient	Date of Transplant	Donor	Day of Leak Dx. Post-Tx.	Function	Cause	Treatment	Results
1	D.J.	1969	LR	1	immediate	Technical failure at ureteral implant site.	Ureteral cath. and nephrostomy	Good
2	M.C.	1969	LR	1	immediate	Technical failure at ureteral implant site.	Re-exploration and re-implantation with ureteral cath.	Ureteral obstruction 4 months following closure of leak—successfully repaired.

related to anastomotic leakage and that was successfully corrected (Patient J.I.). These nine patients represent the only early or late complications from the anastomosis.

Table 2 summarizes the complications seen following ureteral implantation in this series. Leakage occurred in two instances from the ureteral implant site despite use of a submucosal tunnel and a mucosa-to-mucosa anastomosis with fine chromic sutures. These kidneys were salvaged, but one patient did develop late ureteral obstruction.

The two patients who developed complications of the urinary tract not directly related to the anastomotic technique are presented in Table 3. In one the diagnosis of renal tuberculosis was not made prior to autopsy. The other leak was due to perforation of the recipient ureter during a retrograde catheter study for evaluation of oliquria. In both instances, the graft and patient were lost.

Of the 11 patients who developed anastomotic leaks, eight were successfully controlled and only one patient expired from complications directly related to anastomotic failures.

Discussion

Pyeloureterostomy or ureteroureterostomy offer several advantages in the reconstruction of the urinary tract in renal transplantation when compared to the ureteroneocystostomy as judged from our experience and that reported by others.[1-3,7,10,11,13,14,17,19] There is a decreased incidence of inadequate blood supply to the ureter, late obstruction, and the prolonged use of decompressive catheters is avoided.[10-12] The bladder is not opened and dissection around the bladder is not necessary. There is rarely any significant hematuria.[11,17] Retrograde studies are easier to obtain immediately postoperatively and there is no problem with postoperative reflux provided the recipient had non-refluxing ureters prior to transplantation.

Ureteroneocystostomy is the procedure recommended by most authors due to the reported incidence of up to 50% early anastomotic leakage with pyeloureterostomy or ureteroureterostomy. Another major criticism is the reported salvage of less than 50% of kidneys following anastomotic leakage when the donor ureter has been discarded.

In 114 transplants where pyeloureterostomy or ureteroureterostomy was the reconstructive procedure, nine leaks occurred from failure of the anastomosis or a 7.9% complication rate from anastomotic leakage. There were no other complications directly related to the procedure in the early or late postoperative periods. Since 1969 only four leaks have occurred in 79 transplants where this procedure was used (Table 4).

Six of the nine transplants were successfully salvaged by appropriate surgical techniques. Three were controlled by retrograde catheter drainage and three required corrective surgical procedures that included resuturing of the anastomosis, ureteral stents, and nephrostomy drainage. Only one patient died as a result of the failure of the anastomosis. If the recipient ureter is too short for a reconstructive repair following leakage of the anastomosis, the opposite ureter can be brought across as recommended by Leadbetter.[11] This technique was successfully used in one patient. The described technique can also be adapted to a double collecting system either by pyeloureterostomy as described by Feldborg[4] or the combination of a pyeloureterostomy and ureteroureterostomy that was successfully used in one patient in this series.

TABLE 3. *Urinary Tract Fistulas Not Directly Related to the Pyeloureterostomy Failure*

No.	Patient	Date of Transplant	Donor	Day of Leak Dx. Post-Tx.	Function	Cause	Treatment	Results
1	P.P.	1968	C	108	immediate	Necrosis of the calyces. Diagnosis of severe renal necrosis secondary to tuberculosis made at autopsy.	Excision of necrotic calyceal tissue and repair with nephrostomy drainage.	Graft and patient lost due to miliary tuberculosis.
2	L.S.	1972	C	14	delayed	Retrograde cath. perforation of ureter.	Multiple attempts at closure of ureteral defect over ureteral stents with nephrostomy drainage.	Unsuccessful due to inability to control leakage. Pt. returned to hemodialysis.

TABLE 4. *Pyeloureterostomy Anastomotic Leaks Before and After December, 1969*

	Number of Pyeloureterostomies	Number of Anastomotic Leaks	Percentage of Primary Anastomotic Failures
Sept. 1967 to Dec. 1969	35	5	14.3%
Jan. 1970 to Dec. 1973	79	4	5.0%
Total	114	9	7.9%

Two of the nine leaks (No. 3 & 7, Table 1) followed re-exploration of the transplant wound for hemorrhage from the graft. Neither patient had evidence of leakage prior to exploration and it was concluded that the anastomoses were probably disrupted during the exploration procedure. We therefore emphasize the importance of carefully avoiding the area of the anastomosis if re-exploration is necessary during the early healing stages.

Our experience with the ureteroneocystostomy is limited to a relatively small number of patients, and we have experienced three major complications directly related to the procedure in two patients. Both grafts were salvaged but the morbidity and period of hospitalization were similar to that of the pyeloureterostomy failures.

We agree with Starzl,[17] Belzer,[2] and others[1,6,9,13] that ureteral implantation may be the safest technique when performed by surgeons without experience or instruction in the details of successfully constructing a pyeloureterostomy or ureteroureterostomy. In our series, however, it has proven to be an excellent method of urinary tract reconstruction offering certain advantages over ureteral implantation.

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Effects of Cortisone Acetate, Methylprednisolone and Medroxyprogesterone on Wound Contracture and Epithelization in Rabbits

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Standardized flank wounds were made on 20 rabbits divided into the following five groups: Group 1 served as controls, Group 2 were given cortisone acetate 6.25 mg/kg/day (I.M.), Group 3—methylprednisolone (Solu-Medrol) 1 mg/kg/day, Group 4—medroxyprogesterone (Depo-Provera) 35 mg/kg/day, Group 5—methylprednisolone 1 mg/kg/day and medroxyprogresterone 35 mg/kg/day. Wound contracture and epithelization was measured by planimetry of photographs taken twice weekly; weekly weights were recorded, and the maturation phase of wound healing followed in the control and methylprednisolone groups. All three steroids prolonged the latent phase of wound healing, slowed the rate and decreased the total amount of contracture. Cortisone showed the most inhibition of wound contracture and was the only steroid to inhibit epithelization suggesting it may have a slightly different or more potent mode of action. When the methylprednisolone group was followed for seven weeks on daily injections, the maturation phase of wound healing was inhibited, and this inhibition persisted during the next nine weeks after the drug was withdrawn. Only the control and the medroxyprogesterone group gained weight. Combining medroxyprogesterone and methylprednisolone resulted in the severest weight loss of 20% with a 60% mortality.

RETARDATION of wound healing is just one of the many recognized deleterious effects of corticosteroids. Previous workers have shown that cortisone decreases the tensile strength of healing wounds,[4,9,18,30] and as well inhibits contracture[2,12,28] and delays epithelization.[12,29]

The purpose of these experiments is to compare the effects of cortisone acetate, methylprednisolone (Solu-Medrol), and medroxyprogesterone (Depo-Provera) on wound contracture and maturation, epithelization and general metabolism.

In this study, wound healing may be defined as the healing of a surgically incised open wound by secondary intention, i.e., by granulation and epithelization, the resulting decrease in wound size being referred to as contracture. Maturation is that period in wound healing after which the scar assumes its smallest dimensions and epithelization in our study was recorded as the time taken for complete epithelial coverage of the wound.

Methylprednisolone sodium succinate (11B, 17, 21-trihydroxy-6α-methylpregna-1, 4-diene-3, 20-dione, 21-sodium succinate) is essentially the 6α methylation of prednisolone and has greater anti-inflammatory properties though weaker electrolyte regulating effects than prednisolone.[7]

Medroxyprogesterone acetate (17·hydroxy-6α methylpregna-4-ene-3, 20-dione, 17 acetate) is a progestational agent having a steroid structure resembling cortisone and possessing some of the latter's corticosteroid properties. Camanni *et al.*,[1] showed that medroxyprogesterone was capable of supporting life in five adrenalectomized females, but was not effective if the ovaries were removed. Glenn *et al.*,[6] have shown in rats that medroxyprogesterone is a stronger adrenal suppressor than hydrocortisone. It has a proven glycogenic activity in rats[6] and humans, being reported to produce diabetes occasionally when used as a contraceptive.[22] It has an anti-inflammatory effect when injected locally into the croton oil

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induced granuloma of the hamster cheek pouch,[6] but has no effect when given systemically.[6] Its effect on metabolism is difficult to interpret, some groups finding it catabolic,[20] others anabolic.[22]

Medroxyprogesterone has been used in the treatment of carcinoma of the uterus,[13] breasts,[24] and kidney,[20] in the treatment of sexual precocity,[8] and as a contraceptive.[22,27] Medroxyprogesterone has been shown to have immunosuppressive properties[16] as it will suppress antibody response to bovine serum albumin[10] and it prolongs renal canine allograft survival alone or in combination with azathioprine.[15,16,25,26]

Method and Materials

Twenty young New Zealand white rabbits, 3–4.5 kg were divided into five groups of four rabbits each. Each group had approximately the same average weight and a male to female ratio of 3 to 1. All were kept in individual cages and fed Purina rabbit chow and water ad lib.

Group 1—4 rabbits served as controls and received no drugs.

Group 2—4 rabbits were given cortisone acetate 6.25 mgm/kg/day intramuscularly (i.m.).

Group 3—4 rabbits were given methylprednisolone 1 mgm/kg/day (i.m.).

Group 4—4 rabbits were given medroxyprogesterone 35 mgm/kg/day (i.m.).

Group 5—4 rabbits were given methylprednisolone 1 mgm/kg/day (i.m.) and medroxyprogesterone 35 mgm/kg/day (i.m.).

In accordance with a fairly well standardized procedure,[12,14,23] on day zero, the day of wounding, each rabbit was anesthetized with intravenous sodium pentobarbital. After the backs and flanks of the animals were shaved, four squares each measuring 2 × 2 cm were outlined in ink on the exposed backs, two squares being located on each side of the midline (Fig. 1). The inked outlines were photographed and while the animals were still anesthetized, the squares of skin were removed exposing the panniculus carnosus and then the wounds were rephotographed. No ligatures were used. The only major deviations from the standard procedure were to commence drugs on the day prior to wounding, rather than the day of wounding, and to leave the wounds exposed during the entire experiment which some investigators have not done.

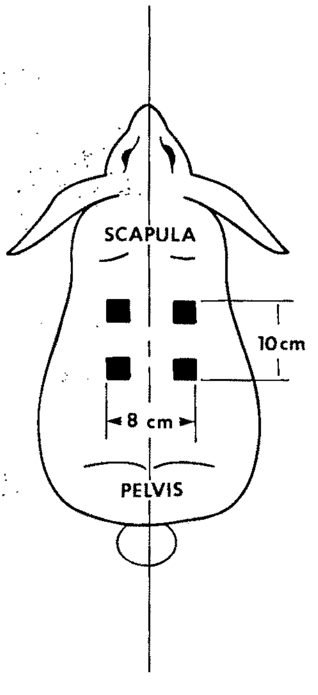

FIG. 1. Squares were placed to be evenly distributed and to occupy a position midway between scapula and pelvis.

Anesthesia was used each time the rabbits were photographed to ensure there would be no change in skin tension from day to day which might affect wound size. The progress of wound contracture was recorded by photographs taken of all groups on days 3, 6, 10, 13, 17, 20, 24, 27, and 31; while on day 38 only Group 1 and on days 34, 38, 41, 44, 48, 109, and 112 only Group III were photographed in order to document the maturation phase in these two groups. Weekly, each rabbit was weighed and daily drug dosages adjusted accordingly. All drugs were continued daily throughout the experiment with the exception of methylprednisolone in Group III which was stopped on day 48.

All photographs were taken with a 35 mm Pentax Spotmatic camera using a closeup lens and Tri-X film. A frame attached to the camera maintained a constant focal distance of 26 cm from the wound to the film. A cm scale next to the wound further insured that all prints obtained would be of the same scale.

Planimetry of the photographs was used to determine wound area which was then expressed as a percentage of the original inked outline. As each group of four rabbits had sixteen wounds, the recorded findings were an average of these sixteen percentages.

Complete epithelization was taken as the day on which the eschar was completely removed from the wound. As the eschar was loosened either by wound contracture or undergrowth of epithelium, it was debrided.

Results

The results are based on an experimental period of 31 days with the exception of that part of the experiment concerned with maturation in which Group I was followed to day 38 and Group III to day 112.

Wound Contracture

The results are summarized in Fig. 2.

Group I (Controls). After excision of the wound, there was an immediate retraction of the edges resulting in a 46% increase in wound area. This early increase rapidly

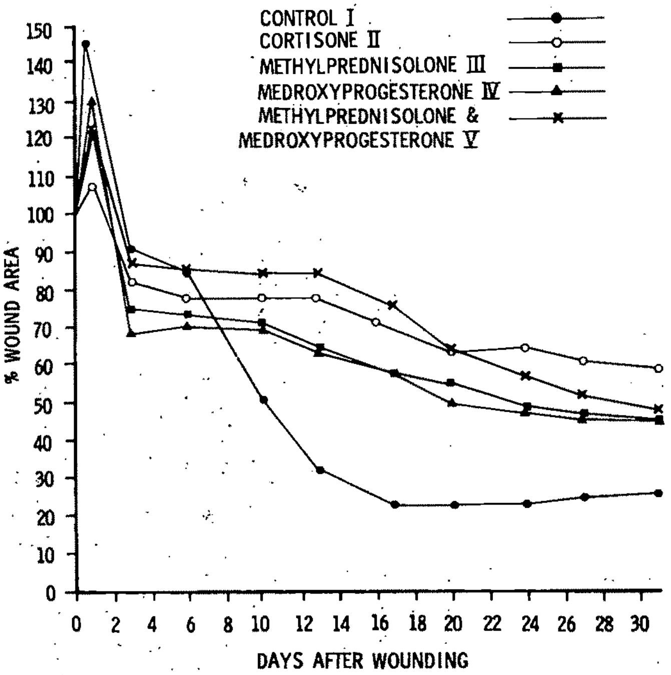

FIG. 2. Graph comparing rate of wound contracture in the five groups of rabbits. All steroid treated wounds have a prolonged latent phase and a decreased contraction when compared to controls. Cortisone treated wounds contract to only 59% of original size by day 31, whereas wounds treated with methylprednisolone, medroxyprogesterone, or a combination of both contract to approximately 45% during the same interval.

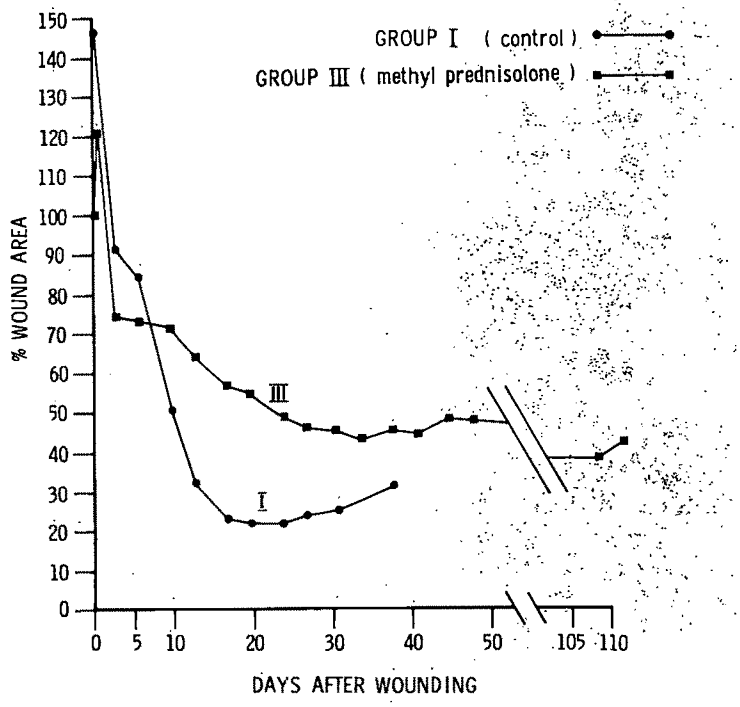

FIG. 3. Graph comparing wound contracture and maturation in control and steroid treated wounds. Control wounds after a maximum contracture to 22% of original area expand to 31% by day 38. In methyl prednisolone treated wounds no late wound expansion is seen even when the steroid is stopped at day 48 and the wounds are remeasured at day 109 and 112.

disappeared as the wound decreased in size to slightly less than normal by day 3. There followed a latent period up to day 6 before the actual contracture of the wound occurred reaching a maximum of 22% of original size by day 17.

Group II (Cortisone). There was a marked prolongation of the latent period up to day 13, more than double that of the control. The degree of contracture was significantly less than the controls through the period from day 10 to day 31 and reached only 59% of the original wound area by day 31. Significance is recorded in the results when $P < 0.05$.

Group III (Methylprednisolone), Group IV (Medroxyprogesterone). The findings were very similar in Groups III and IV, their curves on Fig. 2 being almost identical. There was a prolongation of the latent period in both groups to day 10 and both reached a maximum contracture of 45% of original size by day 31. In Group III, the degree of contracture from days 13 to 31 was significantly different from controls, and days 10 to 31 was significant in Group IV.

Group V (Methylprednisolone and Medroxyprogesterone). Initially there was very little reduction in wound area until the end of the latent period on day 13. At this time, the wound was at 85% of the original area. The ensuing contracture was quite marked reaching an area of 47% of the original size by day 31. Again the differences were statistically significant from controls over the days 10 to 31.

Wound Maturation

Group I (Control). (See Fig. 3). After a maximum contracture to 22% of original pre-wound area by day 17, the area gradually increased to 31% by day 38. During the maximum contracture (day 17) the scars assumed a stellate appearance (Fig. 4). By day 38 the arms of the stellate had considerably increased in length. The net effect was to increase the area of the scar only slightly (from 22% to 31%) while almost doubling the perimeter in relation to its size on day 17.

Group III (Methylprednisolone). After a maximum contracture to 43% of original area by day 34, the wounds treated with methylprednisolone showed no tendency

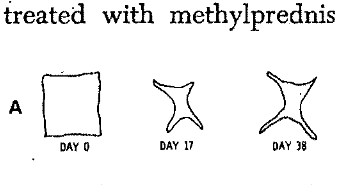

FIG. 4. Illustrates the typical appearance of control and steroid treated wounds during the period of study. A. Wounds of control (Group 1) animals during maximum contraction day 17) assume a stellate appearance which becomes more exaggerated in the maturation phase. B. In contrast methylprednisolone treated wounds both reach a lesser degree of wound contraction and even when followed for 112 days have little tendency to mould into a stellate configuration.

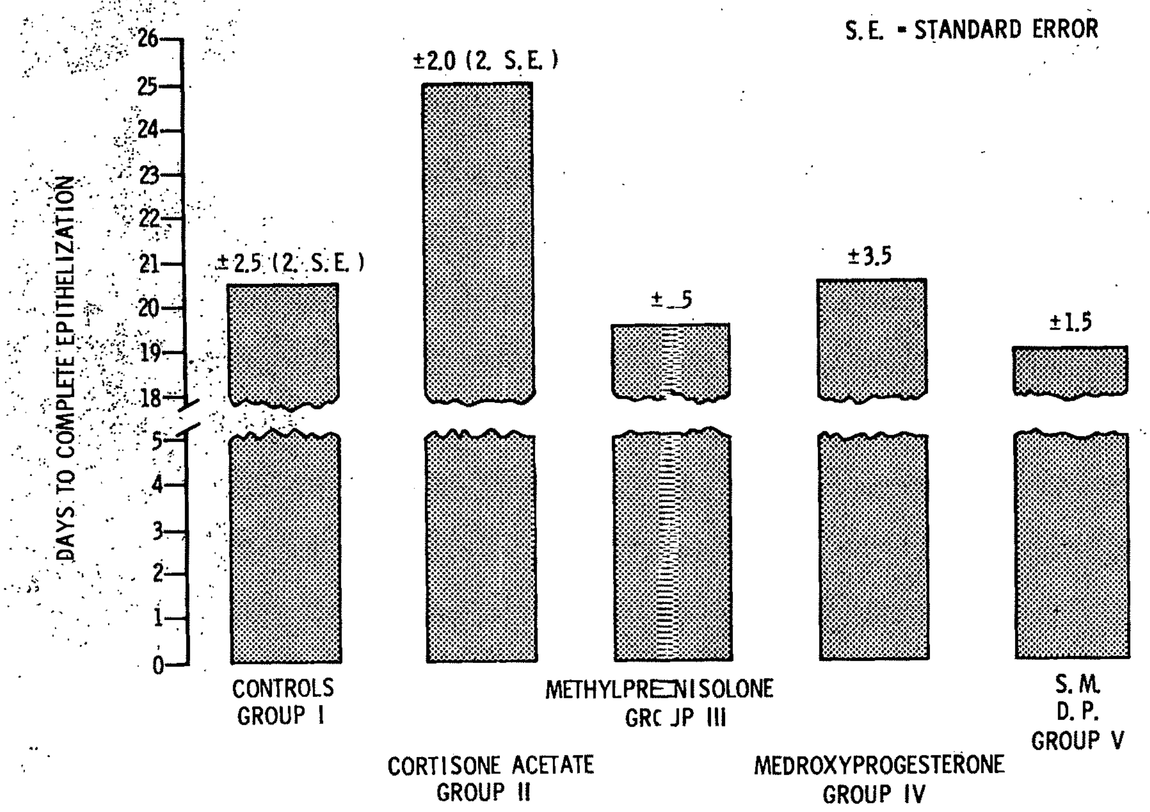

FIG. 5. Average time to complete epithelization of 16 wounds in each group of rabbits. Only those wounds treated with cortisone acetate show significant delay in epithelization. The figures at the top of each column represent 2 standard errors. abbr. methylprednisolone, S.M. and medroxyprogesterone, D.P.)

towards expansion or increasing their perimeter even when the animals were kept on methylprednisolone for 48 days. In an effort to see if the lack of significant wound enlargement was due to the continued presence of methylprednisolone, the drug was discontinued and after 60 days the animals were re-photographed, on day 109 and 112. On day 109 the wound area was 38% of the original size and 42% on day 112, the scar at this time having a rudimentary semblance of a stellate configuration with only minor increases in its perimeter when compared to controls (Fig. 4B).

Epithelization

The results are summarized in Fig. 5.

Epithelization in the control group was complete in an average of 20.5 days in the 16 wounds. Those animals on cortisone acetate were the only group showing a significant delay in epithelization, taking an average time of 25 days. Group III (methylprednisolone) took 19.4 days, Group IV (medroxyprogesterone) took 21 days and Group V took 19 days to complete.

Metabolic Effects

The results are summarized in Table 1. Only the control (Group I) and the animals on medroxyprogesterone showed weight gain over the 31 day period, all other groups losing weight. Group V on methylprednisolone and medroxyprogesterone had a 20% decrease in body weight (actually a 30% decrease when compared to controls) and showed rather marked side effects such as a very noticeable loss of muscle bulk, loss of hair, droopy ears and general emaciation.

Mortality (Table 2). The results on wound contracture, maturation, and epithelization are based on 20 animals out of an original total of 25 rabbits. The four rabbits dying during the experiment were excluded from the results. As there were five animals left in Group IV at the end of 31 days, it was necessary to exclude one rabbit at random to reduce the number in that group to four.

TABLE 1. *Average Change in Weight From Day 0 to 31 in Each Group of Four Rabbits*

Group I	Control	11% increase
Group II	Cortisone acetate	7% decrease
Group III	Methylprednisolone	4% decrease
Group IV	Medroxyprogesterone	7% increase
Group V	Methylprednisolone Medroxyprogesterone	20% decrease

TABLE 2. *Mortality of 25 Rabbits Over a Period of 31 Days*

Group I	No deaths out of four animals
Group II	One death out of five
Group III	No deaths out of four
Group IV	One death out of six
Group V	Two deaths out of six

In Group V, two additional rabbits were dead by day 33

All deaths were attributable to pulmonary infections which seemed to be particularly prevalent in those groups losing weight. One wound infection occurred and that was in the animal which died in Group II. It is noteworthy to mention that two additional rabbits died in Group V just following the conclusion of the experiment—giving this group a mortality of 66% by day 33.

Discussion

Luccioli divides normal wound contracture into five phases[14] which are illustrated by the control group in Fig. 2:

Phase 1. Immediate retraction of the wound edge, probably caused by the inherent elasticity of the surrounding skin;

Phase 2. Early decrease, from ½ hour to day 3, possibly due to the dehydration of the eschar;

Phase 3. A latent period, up to day 6;

Phase 4. Actual contracture, day 6 to 17; and

Phase 5. Scar maturation, from day 17 onward, the gradual expansion or moulding of the wound probably related to the pull of the surrounding tissue on the maturing scar.

As a group, the steroids affect all five phases of wound contraction (Fig. 2). The immediate retraction is inhibited, and the early decrease in wound size (Phase 2) is enhanced. The latent period is prolonged, and the phase of contracture is both prolonged and of less magnitude when compared to controls. In Group III (methylprednisolone) there appears to be a loss of the normal scar maturation phase. This finding is probably typical for all corticosteroids as they appear to interrupt the abnormal maturation phase of keloid formation in humans.[19] The inhibition of the maturation phase appears to be irreversible, even when methylprednisolone was discontinued on day 48 in Group III, there was no appreciable increase in scar area by day 112 and only minor alterations in shape.

Within the steroid group, two main patterns emerged (Fig. 2), that of medroxyprogesterone treated animals (Group IV) and that of cortisone treated animals (Group II). The wounds treated with medroxyprogesterone have a more marked early decrease (Phase 2), a shorter latent period (Phase 3), and a more marked scar contraction (Phase 4) than those wounds treated with cortisone. The medroxyprogesterone treated wounds show a statistically significant difference in contracture from the cortisone treat group ($P < 0.05$) during the days 10 to 24.

Wounds in animals treated with methylprednisolone (Group III) responded so similarly to those treated with medroxyprogesterone (Group IV) that a common mechanism of action could be postulated, their graphs on Fig. 1 are almost identical. Due to an increase variability of wound contracture within Group III animals, there was no significant difference ($P < 0.05$) when compared to cortisone treated animals of Group II. However, there are several findings to suggest that there is a significant difference between methylprednisolone and cortisone acetate. 1) The dosages of methylprednisolone and cortisone acetate are considered to be equivalent and yet in Fig. 1, their graphs are certainly not identical. (1 milligram of methylprednisolone is the anti-inflammatory equivalent of 6.25 milligrams of cortisone acetate[7]); and 2) Cortisone acetate is the only steroid in this experiment to significantly inhibit epithelization of wounds.

Group V (Methylprednisolone and Medroxyprogesterone). Initially wound healing is very retarded and this in some way may be related to the marked catabolic effect of combining these two drugs. In Group V, the early decrease (Phase 2) and the latent period of wound healing is prolonged to the same or greater extent than in the cortisone treated animals; however, the actual contracture phase is much greater than in the cortisone group. The final contracture at 31 days is within a few degrees of that found when methylprednisolone or medroxyprogesterone was used alone. The inhibitory effects of two drugs have been added in Group V and yet results in less wound contracture than found in cortisone treated wounds. This enhances the suggestion that either cortisone is a very much more potent inhibitor of wound contracture than either methylprednisolone or medroxyprogesterone, or that it has a slightly different mode of inhibition.

It has been already established that cortisone inhibits contracture, epithelization, and tensile strength in healing wounds. Since medroxyprogesterone and methylprednisolone appear to have significantly less effect than cortisone on both contracture and epithelization, it seems reasonable to assume that they would also have less effect on the development of tensile strength. However, it must be borne in mind that contracture and tensile strength are not exactly comparable processes as tensile strength over the first few weeks is proportional to the collagen content,[17] whereas normal contracture may occur in scorbutic wounds.[28] Epithelization seems to be related more to the development of tensile strength as Vitamin A has the ability to reverse cortisone's inhibitory effect on epithelization[12] and the development of tensile strength[3,4] but has no effect on cortisone's inhibition of wound contracture.[23]

Though medroxyprogesterone has a similar action on the contracting wound as methylprednisolone in our experiment, it has no clear anabolic or catabolic effects. Cortisone and methylprednisolone cause a weight loss of 7% and 4% respectively; those animals on medroxyprogesterone gained 7% in comparison to a control group whose gain is 11%. The combination of methylprednisolone and medroxyprogesterone in Group V proved almost disastrous with a 20% weight loss. The marked catabolic effect of medroxyprogesterone when used in combination with a corticosteroid has been previously noted when it was used with cortisone by Hulka.[11] This finding may be peculiar to rabbits as it has not been found to be true when medoxyprogesterone and prednisone were used in combination in renal transplant recipients (A. S. MacDonald, personal communication).

Keloid or hypertrophic scar formation in man occurs 3–5 weeks following wounding and is probably due to an abnormality of collagen metabolism in the maturation phase of wound healing.[19] Keloids are not known to occur in animals and because of this, there is a lack of experimental evidence in the treatment of this condition. The finding that methylprednisolone appears to inhibit the maturation phase of wound healing in rabbits may be related to the ability of corticosteroids to inhibit keloid formation in humans, and an interesting experimental model could be employed to compare the relative merits of the different steroids in the treatment of this condition. With reference to this paper, cortisone acetate appears to inhibit all phases of wound contracture more than methylprednisolone and this is probably true in relation to its effect on the scar maturation phase as well.

Corticosteroids probably inhibit wound healing primarily by delaying the migration,[5] multiplication,[5] and maturation of fibroblasts.

Ehrlich[5] and Sandberg[21] in experiments on collagen content and tensile strength of healing wounds have suggested that the inhibitory effect of corticosteroids occurs primarily during the period of inflammation, i.e. just following wounding. They measured collagen content and tensile strength of rat wounds at the end of one week which is probably too early to measure anything but the processes which have occurred during the inflammatory phase and thus their conclusions deal only with this phase. McNamara[18] followed his animals for six weeks and showed that wounds in animals given steroids during the period of inflammation had normal tensile strength by this time. Stephens[23] similarly showed that steroids given after the completion of the inflammatory phase caused inhibition of wound contracture to almost as great an extent as wounds treated with steroids during the inflammatory phase.

To say that corticosteroids inhibit wound contracture by inhibiting inflammation is probably a gross over simplication of this process. In our experiment, although anti-inflammatory equivalent dosages of methylprednisolone and cortisone acetate were used, the latter showed more inhibition of wound contracture which further suggests that steroid inhibition cannot entirely be relegated to the initial inflammatory phases of wound healing. By slowing down the migration and multiplication of fibroblasts into the wound area, corticosteroids probably prevent a significant number of fibroblasts from maturing to form collagen and thereby decreasing the tensile strength of the healing wound, while the actual inhibition of migration and multiplication of the fibroblasts is probably related more to the inhibition of wound contracture. However, much of this is still conjecture.

Conclusions

Methylprednisolone, medroxyprogesterone and cortisone acetate all prolonged the latent period of wound healing and both prolonged and decreased the magnitude of the phase of contracture.

Methylprednisolone and medroxyprogesterone inhibit wound healing less than cortisone acetate, though only in the medroxyprogesterone group of rabbits was this significant. This and the finding that cortisone acetate was the only steroid to inhibit epithelization suggests that the latter may have a slightly different or more potent mode of action.

Methylprednisolone inhibited the maturation phase of wound healing and this has felt to be typical of most corticosteroids.

Medroxyprogesterone in a dose of 35 mg/kg appeared equivalent to 1 mg/kg of methylprednisolone in its effect on wound healing except that it was not catabolic. This advantage may be outweighed by the necessity to give this drug by injection. The catabolic properties of methylprednisolone were potentiated by the addition of medroxyprogesterone and four out of six animals died in the group which received this combination.

The suggestion is made that the inhibitory effects of corticosteroids on wound healing cannot be entirely based on their anti-inflammatory properties.

Acknowledgments

The authors would like to thank the Preventive Medicine Department of Dalhousie University for help in statistical analysis of the results.

In this experiment, cortisone acetate was provided by Merck, Sharp and Dohme in the form of 10 cc vials containing 50 mgm/cc. Medroxyprogesterone was provided as Depo-Provera, 400 mgm/cc and methylprednisolone as Solu-Medrol, 40 mgm/cc from the Upjohn Company.

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Laser Surgery in Exsanguinating Liver Injury

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Thirty-two conditioned 15–18 kg dogs underwent laparotomy, heparinization, left lateral hepatic lobe injury, and subsequent partial left lateral hepatic lobectomy. The hemostatic capabilities of the surgical scalpel combined with suture ligatures and stay sutures, the Bovie, and the CO_2 laser were compared. The CO_2 laser proved significantly more effective in achieving hemostasis both in comparison to the Bovie and the surgical scalpel combined with classical methods. The postoperative mortality utilizing the Bovie was 11%, the scalpel 30% and the laser 23%. Two of the three laser deaths were related to a bulky laser delivery system which can be redesigned. Postoperative laboratory evaluation revealed that SGOT, LDH, alkaline phosphatase, total protein, albumin and hemoglobin levels were altered in the postoperative period but returned to normal levels in uniform fashion in all groups. There was no statistical difference between various surgical modalities with regard to these parameters. The white blood count was significantly lower in laser dogs when compared to the other two groups. Other laboratory parameters were unchanged. Damage to liver tissue may be less extensive when the laser is utilized as opposed to the Bovie or stay suture methods of hemostasis and healing is equally good. The CO_2 laser is considered a valuable ancillary tool in hepatic resection and clinical evaluation is warranted.

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ACUTE HEPATIC INJURY carries a high mortality. Edler[1] in 1887 reported 540 cases of hepatic injury treated without surgery with a resulting mortality of 66%. Despite attempted surgical repair, hepatic injuries also carried a 66% mortality during World War I. The advent of antibiotic therapy, refined surgical management, and decreased time lag from injury to surgical exploration, reduced the mortality of World War II hepatic injury to 27%.[6] More recently, hepatic injury has carried a 10–18% overall mortality with two basic injury groups being identified; those with relatively minor trauma represented by the simple stab wound and those with severe blunt trauma resulting in a crush injury. The mortality of the former is 3–4%, where the latter approaches 45%. In the crush injury, various treatment modalities have been utilized often with a degree of futility. These have included gauze packs, simple wound closure, suture ligation of blood vessels and bile ducts, suture of hemostatic agents to the wound surface and biliary decompression. In the last ten years total anatomic hepatic lobectomy has become popular in the treatment of massive liver injury. Pinkerton reported a 23% mortality following anatomic hepatic lobectomy for both trauma and elective procedures.[8] The incidence of major complications following such surgery remains, however, at 50%. Clearly a better method for the treatment of hepatic trauma is needed.

Since the first laser was produced in 1960, this concept of light energy has undergone rapid development. Today the CO_2 laser operating at a wave length of 10.6 microns can be used as a reliable cutting instrument, and can be delivered to an operative field in sterile fashion. Preliminary studies in our Laser Laboratory[2,3,10] and elsewhere[4,5,8] during the past three years indicate that this laser, used as a cutting instrument, has hemostatic qualities which shorten the time of hepatic surgery and decrease morbidity and mortality.

The recent clinical success of carbon dioxide laser excision of 25 acute burned patients followed by immediate autografting has encouraged us to explore the use of this instrument to control hemorrhage in other lesions. We have started in the laboratory to establish the safety of this instrument to control oozing from the cut surface of the canine liver following partial lobectomy or debride-

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nent of devitalized liver tissue. The marked variety of iver lesions that occur in traumatically injured patients nake a clinical comparitive study almost impossible, and require the laboratory milieu to establish a standardized crush hepatic lesion.

Equipment

An experimental American Optical Corporation coninuous wave surgical CO_2 laser with a manipulating arm capable of transmitting an 80 watt focused beam o the operative field was used. Surgical cutting was perormed using a beam focused to a diameter of 1 mm vith an output range of 45–80 watts (6–12 Kw/cm²). Surface coagulation was performed using an unfocused beam with a diameter of 10 mm at the same outputs (50–00 w/cm²). Delivery of the laser beam was controlled vith a foot switch and the output power was varied by means of an autotransformer.[9]

Methods

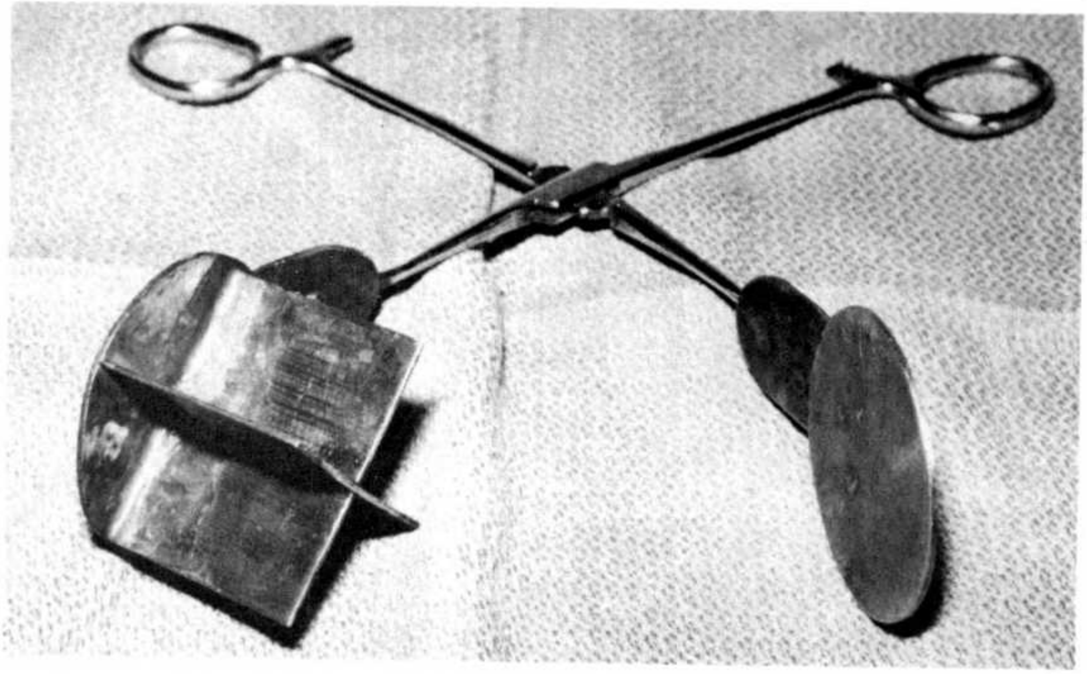
Conditioned female dogs weighing 15–18 kg were nesthetized with intravenous pentobarbital 6.5 mg/kg nd ventilated with a Harvard respirator through an ndotracheal tube. Blood loss was replaced with Ringer's actate solution in the amount of 2 cc for each 1 cc blood oss and tetracycline 250 mg was administered intraenously both during surgery and again on the first postperative day.

In all dogs, the left lateral hepatic lobe was crushed nd then excised to simulate the clinical situation of rejected blunt trauma. The crush injury was made with the instrument shown in Fig. 1. Despite heparinization (100 u/kg) the crush injury alone was not a uniformly fatal injury. However, excision of the injured portion of the lobe without further hemostatic measures resulted in a 100% mortality regardless of whether the laser, the Bovie, or the scalpel was used as the cutting instrument.

The control group (I) was comprised of six dogs. Each dog underwent laparotomy through a right paramedian incision, was heparinized with 100 u/kg sodium heparin, and sustained a uniform crush injury to the left lateral hepatic lobe as described above. The scalpel, the Bovie, and the laser were each used to excise the injured portion of the left lateral hepatic lobe in two dogs. Immediately following such partial hepatic lobectomy the surgical incision was closed without effort at hemostasis. A 100% mortality occurred within 24 hours.

Group II was comprised of ten dogs that underwent laparotomy through a right paramedian incision. The portal vein and hepatic artery were isolated and the dogs were given 100 u/kg sodium heparin. The left lateral hepatic lobe was injured as previously described and subsequently bleeding was allowed to occur for two minutes. Weighed dry sponges were used to absorb and measure the two-minute blood loss. The hepatic artery and portal vein were then occluded and the injured portion of the left lateral hepatic lobe excised with the cold knife, a #10 surgical scalpel blade. The afferent hepatic circulation was released and the blood loss over a second two-minute period measured. The afferent hepatic circulation was again occluded for five minutes during which time initial hemostasis was obtained utilizing individual suture ligation of hepatic vessels and larger more constricting stay sutures. After five minutes

IG. 1. Instrument for eating hepatic injury. lades are 5 cm in length id were not sharpened.



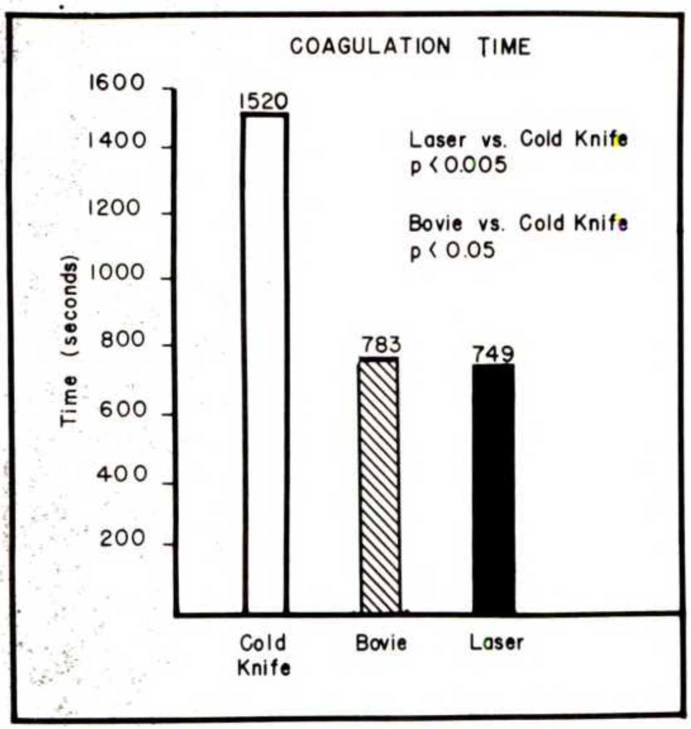


FIG. 2. Coagulation time.

the hepatic circulation was released to allow adequate portal venous return and restore hepatic circulation. Subsequently, placement of suture ligatures and stay sutures continued until complete hemostasis was obtained. Blood loss occurring during the entire period of hemostasis was measured as was the time (in seconds) required to achieve coagulation. No thermal coagulation in any form was used.

Group III was comprised of nine dogs treated exactly as those in Group II except the Bovie was used both to excise the injured tissue and to coagulate small vessels and bile ducts. Suture ligation of blood vessels greater than 1.5 mm in diameter was usually required. Stay sutures were not used.

Group IV was comprised of 13 dogs treated exactly as those in Group III, except the Bovie was replaced by the carbon dioxide continuous wave laser.

During the postoperative period all dogs were evaluated with respect to 20 laboratory parameters which included: WBC, HCT, HGB, partial thromboplastin time, three tube Lee White clotting time, fibrinogen, serum sodium, potassium, chloride, CO_2, glucose, BUN, calcium, phosphorus, total protein, albumin, total bilirubin, SGOT, LDH and alkaline phosphatase. Clotting times were performed preoperatively, one hour postoperatively, and on the first postoperative day. Partial thromboplastin times and fibrinogen were drawn preoperatively and on the first postoperative day only. All remaining laboratory studies were drawn preoperative, and on postoperative days, 1, 3, 7, 14, 21, 35, 42, and 84. Each animal was explored between the 35th and 42nd postoperative day and re-explored on postoperative day 84. At the initial surgery liver biopsies were taken for light and electron microscopy and such sections were repeated at each postoperative exploration. Aerobic and anaerobic cultures were taken of the resected liver tissue at the same times. Cultures were also obtained of all wound infections and liver abscesses when present. Animals which did not survive the postoperative period were immediately autopsied and similar studies performed.

Safety (plastic) glasses or personal prescription glasses were worn by all operative room personnel to protect against CO_2 laser beams. Regular operating room clothing protected personnel against skin burns from non-focused beams. Rarely burns occurred from a focused CO_2 laser beam. These lesions simulated an electric Bovie burn and were treated similarly. A non-explosive anesthetic is used in CO_2 laser surgery.

Results

The time taken to achieve hemostasis is seen in Fig. 2. Hemostasis in the laser and Bovie groups required an average of 12 and 13 minutes respectively. Hemostasis utilizing conventional (non-thermal) methods alone required 25 minutes. This was significantly longer than the time required for the laser and Bovie groups ($p < 0.005$ and $p < 0.005$ respectively). There was no significant difference in the time taken to achieve hemostasis in the laser and Bovie groups.

Figure 3 shows the amount of blood loss for each experimental group during the four periods which it was measured. Blood loss due to the crush injury alone was minimal during the two-minute post injury period and was similar in all groups. Blood loss in the laser group was 11 ml, the Bovie group, 13 ml, and the scalpel group, 18 ml. There was no statistical difference in these figures. The small quantity of blood loss indicates that the model was indeed a crush injury as opposed to one that cleanly lacerated those blood vessels involved, and that the injury in each group was approximately the same.

Blood loss after excision of the injured portion of the left lateral hepatic lobe was 115 ml in the laser group compared to 202 ml in the Bovie group, 227 ml in the scalpel group. The laser, therefore, has significantly superior hemostatic qualities while cutting when compared to the Bovie ($p < 0.025$) and conventional knife methods ($p < 0.001$).

Blood loss during the coagulation period is significantly greater in the scalpel group (142 ml) as compared to the laser group (49 ml) ($p < 0.01$), although statistical difference between the scalpel and Bovie groups (82 ml) cannot be demonstrated. The additional time taken for hemostasis is a definite factor in explaining the increased blood loss when suture ligation methods are used exclusively. A significant portion of the bleeding during this period is from persistent loss from blood vessels with an internal diameter less than 1 mm. Vessels of this size are rapidly coagulated by both the Bovie and laser, however with non-thermal methods, this generalized ooze persists for the entire hemostatic period.

The total operative blood loss with the laser (141 ml) is significantly less than the 353 ml of blood lost with the cold knife ($p < 0.001$) and the 252 ml lost with the Bovie ($p < 0.005$). Statistical difference between the Bovie and cold knife groups was not demonstrated.

When the various laboratory parameters are observed, difference between the groups become less clear cut. Clotting studies reveal that clotting time, fibrinogen levels, and partial thromboplastin times were normal and not significantly different between groups both in the preoperative and postoperative periods. The clotting time one hour postoperatively was greater than 60 minutes in all dogs, demonstrating that adequate surgical anticoagulation had been achieved in all groups. The mean white blood count preoperatively for laser dogs was 10,554, for Bovie dogs 10,450, and scalpel dogs 13,511. Postoperatively however, on day one the mean laser group white count was 23,062, whereas, in the Bovie and scalpel groups it was 33,257 and 31,511 respectively. These values are all statistically different than the respective preoperative levels (Fig. 4). The laser white count was, in addition, notably lower than that of the other two groups during the period from postoperative day one to postoperative day seven. Statistical difference was achieved only intermittently, however, (Fig. 4). When the laser and Bovie groups are compared $p < 0.025$ on postoperative day one and three and when the laser and scalpel groups are compared $p < 0.05$ on day seven. These results suggest that there is less tissue damage and subsequent inflammatory response in the laser treated animals than in the other two groups. This conclusion although supported by our histologic studies is very difficult to document in a more definitive fashion. White blood counts in all groups returned to values not different from preoperative values by day 14.

Hemoglobin values (Fig. 5) dropped significantly from preoperative values in all groups (laser $p < 0.01$, Bovie $p < 0.005$, scalpel $p < 0.001$). The lowest values were achieved between the third and seventh postoperative day. There is no statistical difference, however, in the decrease in hemoglobin when different groups are compared during the postoperative period. Hemoglobin returned to normal by the 14th postoperative day in the Bovie and laser groups and the 21st postoperative day in the scalpel group.

Alkaline phosphatase, total protein, serum albumin, SGOT and LDH each changed significantly from preoperative values in all dogs, but with the exception of SGOT, no significant difference could be demonstrated between groups. SGOT was higher in the Bovie group than the laser group throughout the postoperative period and a $p < 0.05$ was achieved on the third postoperative day. This relationship did not hold for other enzymes studies, however, and to attach clinical significance to the finding is unwarranted. The decrease in albumin and total protein reflect the hemodilution which results from blood loss replacement with Ringer's lactate in a 2:1 ratio. Laser dogs which had the least blood loss and, therefore, the least replacement fluid show no change in total protein levels and a rather minimal change in albumin. All of

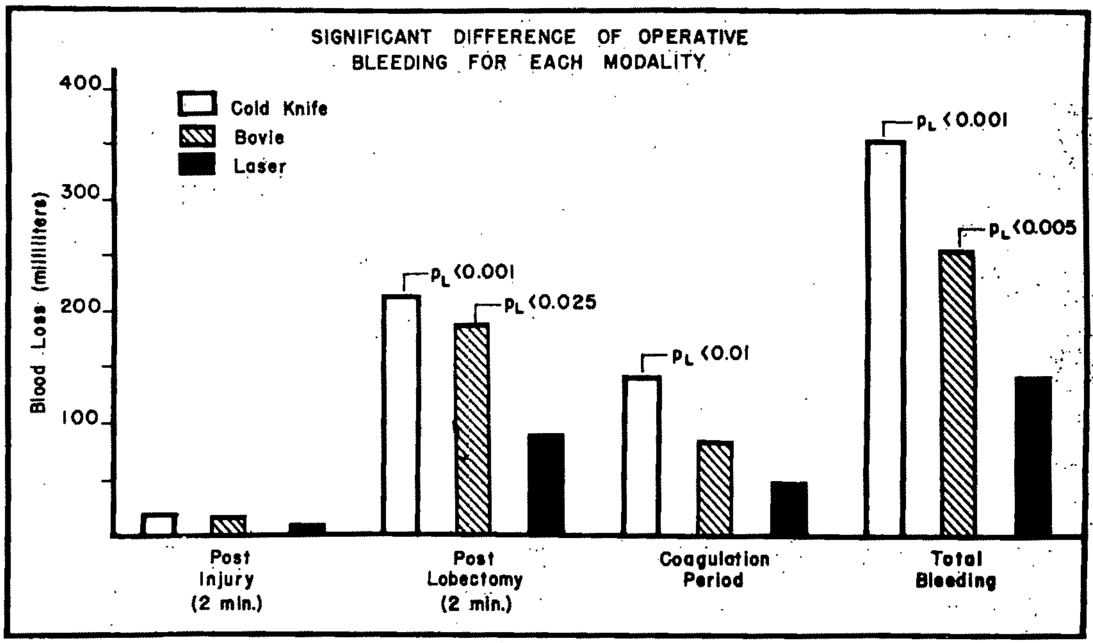


FIG. 3. Bleeding studies. P values shown are cold knife or Bovie group compared to the laser group in each case.

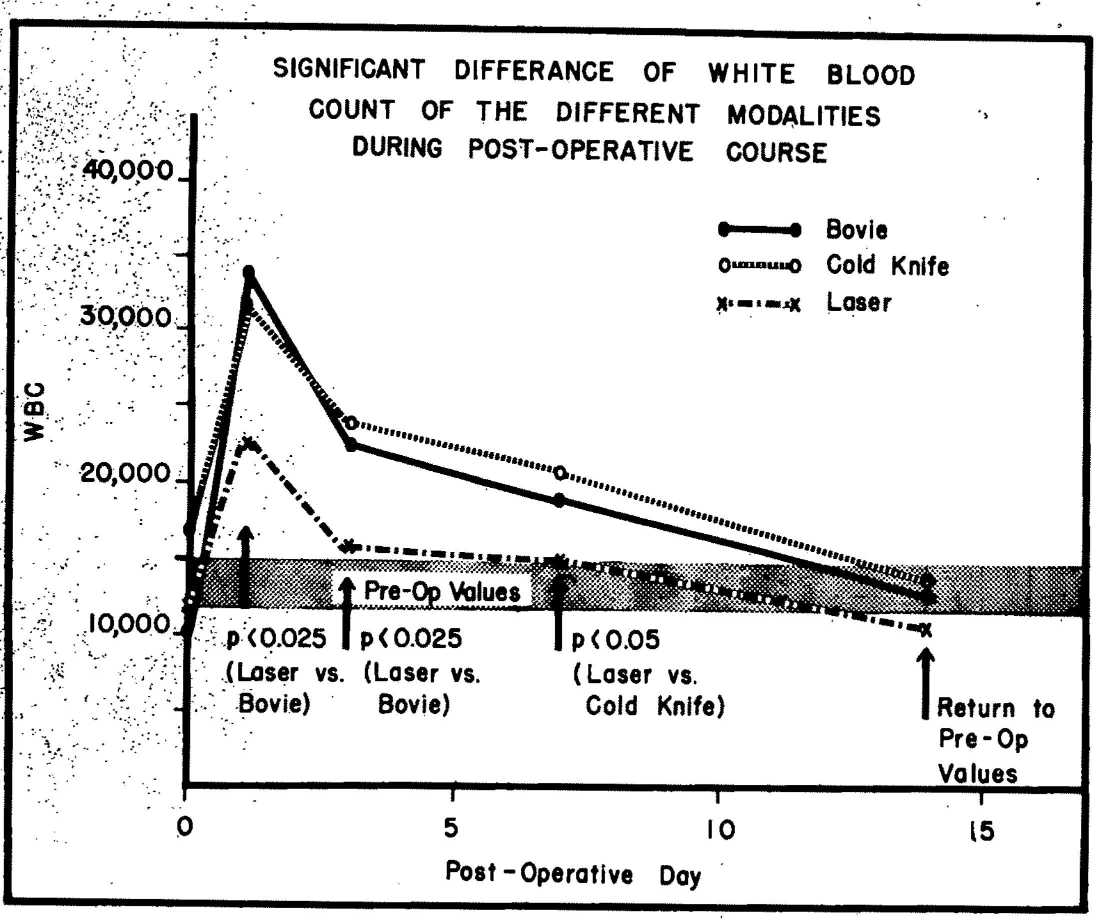


FIG. 4. Comparison of postoperative white blood counts. P values compare differences between the different groups.

these changes are transient with the alkaline phosphatase returning to normal on postoperative days 14–21, total protein on postoperative days 7–14, albumin on postoperative days 7–21, SGOT uniformly on postoperative day seven and LDH on postoperative days 21–35. Sodium and potassium showed a slight decrease on the first postoperative day and then increased to greater than preoperative values after approximately one week as edema fluid was excreted and blood breakdown products were absorbed. Values for these parameters at all times stayed within normal range. Total bilirubin, serum chloride, CO_2 and glucose and BUN did not change significantly in the postoperative period and were at all times within normal range.

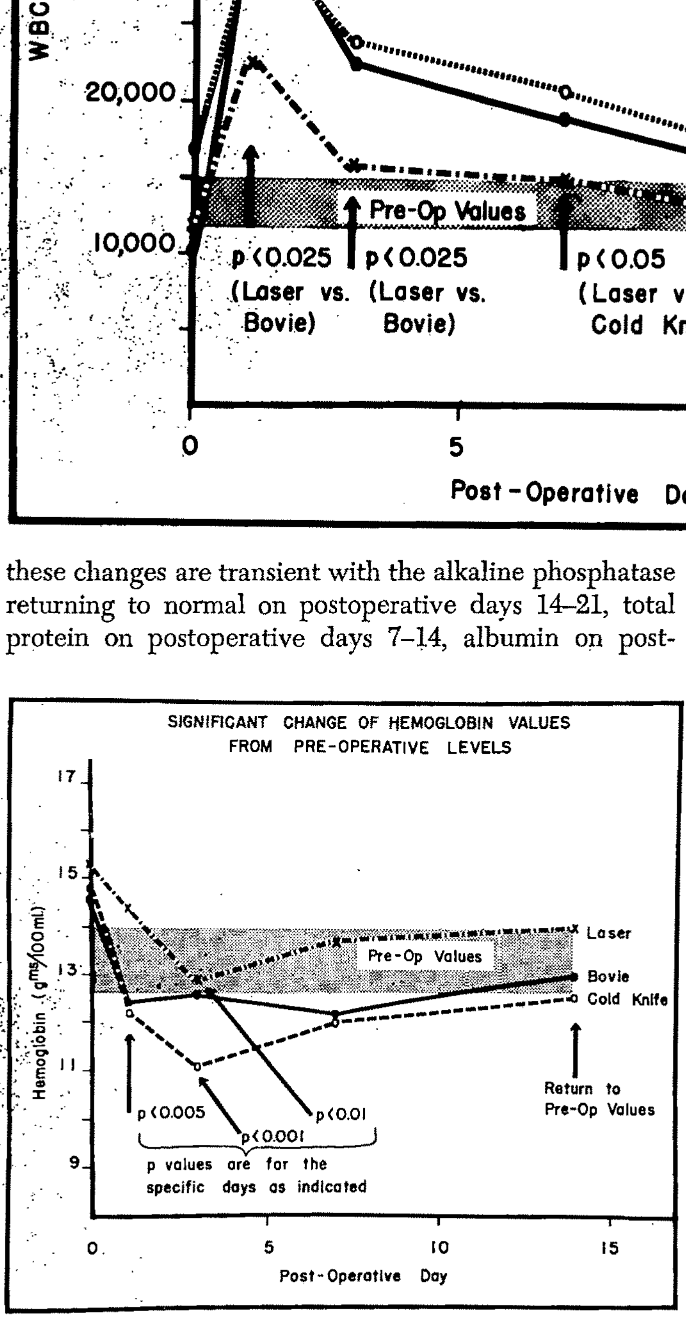


FIG. 5. Comparison of postoperative hemoglobin levels. P values represent significant change from preoperative levels. There is no significant difference between groups.

All surviving animals were re-explored between the fourth and sixth postoperative weeks. At re-exploration little was found to differentiate the experimental groups, with the exception that laser and Bovie dogs had more intraperitoneal adhesions than those dogs in the scalpel group. A small intraperitoneal abscess was found in a single dog in each the Bovie and scalpel groups, however, the abscess did not cause mortality nor did it cause laboratory parameters to be different from other animals in the group.

Bacteriological studies revealed that approximately fifty percent of the animals in each group had positive liver tissue culture growth at the time of the initial surgery. The predominate organisms were *Staphylococcus aureus*, alpha Streptococcus and Clostridial species. The incidence of positive liver culture growth increased at the first re-exploration to 12/13, 5/9 and 9/10 positive culture growth in the laser, Bovie and scalpel groups respectively. Clostridial species, *Staphylococcus aureus* and non-hemolytic (pyogenic) Streptococcus were the most common organisms. No significant difference between groups could be noted. All animals dying of infection revealed a crepitant liver and cultures demonstrated mixed organisms with *Staphylococcus aureus* and Clostridial species being uniformly present.

Histological examination revealed that liver tissue incised and removed with the CO_2 laser and the Bovie could not be differentiated, although both were easily differentiated from tissue incised with the scalpel. Liver tissue incised with the laser and Bovie demonstrated four specific histologic layers. The first or closest to the thermal source was a layer of coagulation necrosis 50 μ thick. The second layer was 200–300 μ thick and contained grossly disrupted cellular architecture with intermingled steam bubbles. The third layer was composed of intact but apparently non-viable cells with homogenous degranulated cytoplasm and was 200–500 μ in thickness. The fourth layer contained normal liver tissue. Electron microscopic sections revealed no difference in the effect of the Bovie and CO_2 laser on cellular ultrastructure. By contrast, liver incised with a scalpel contained a 50 μ thick area of cellular disruption without evidence of steam bubbles, coagulation necrosis or other damage to underlying tissue.

It should be noted that this histologic appearance does not change after thermal *coagulation* has taken place, however the depth of injury does increase. Sections taken from healing liver at four weeks in laser and Bovie dogs confirm this, and demonstrate residual non-viable liver tissue to be 2 mm and 3.5 mm in average thickness in laser and Bovie dogs respectively.

Examination of the 30-day postoperative mortality (Table 1) reveals an 11% mortality in the Bovie group (1 of 9), a 23% mortality in the laser group (3 of 13), and a 30% mortality in the scalpel group (3 of 10). One dog died of infection in each of the laser and Bovie groups and two dogs died of infection in the scalpel group. In addition, one scalpel dog died because of postoperative hemorrhage from the hepatic resection site on the first postoperative day. Of note are two laser dogs which died in the early postoperative period of hemorrhage from liver lacerations on the diaphragmatic liver surface not related to the operative site. These were not recognized at the time of surgery. These injuries result from difficulty in manipulating a still somewhat cumbersome CO_2 laser delivery arm. Efforts were made, therefore, through increased traction and division of the triangular ligament to deliver the liver into the operative field (to meet the laser) with resulting unrecognized injuries to the liver. We feel that such mechanical problems are overcome by the new laser instruments appearing for clinical use which permit more flexibility in the delivery system.

TABLE 1. *30-Day Postoperative Deaths*

	Laser	Bovie	Scalpel
Deaths	3/13	1/9	3/10
Hemorrhage			1
Unrelated Hemorrhage*	2		
Infection	1	1	2

*Postoperative bleeding from the liver at a site distant from the site of hepatic resection.

Discussion

Surgical incision performed with the CO_2 laser is achieved by total absorption of the beam within 200 mμ of the liver surface. This absorbed energy is converted into heat which causes vaporization of the tissue exposed to the focused beam. Temperatures achieved in the zone of incision in soft tissue are not much in excess of 100 C and, because of poor conduction, the heat is primarily dissipated by vaporization of cellular water. The temperature rise in surrounding tissue is therefore quite limited, and amounts to only 15 C for a period of 2–3 seconds at a point 2 mm from the line of incision.[3] This is well within the limits of cell viability and is confirmed by our histologic sections.

The hemostatic qualities of the laser relate to the thin dry coagulum which is formed on the cut surface of the liver as well as protein denaturation in the liver parenchyma itself. In the case of the CO_2 laser this layer of coagulation necrosis is only 0.05 mm thick. The hemostatic strength of this coagulum depends on a firm underlying tissue stroma making the liver an ideal organ for such support. In liver as well as in striated muscle and kidney, vessels up to 1.5 mm internal diameter are well controlled by simple defocused CO_2 laser coagulation. Other laser wavelengths, specifically that the YAG laser at 1.06 μ are being evaluated as to their surgical potential and have been demonstrated to coagulate vessels of larger diameter (3–4 mm) chiefly by deeper penetration of tissue and increased thickness in the layer of cellular disruption and protein denaturation. Such deeper penetration will, however, leave additional necrotic tissue to be cleared in the postoperative period and, therefore, the potential for postoperative infection may be increased. The problem is currently under study.

Suture ligation of blood vessels in small animals such as the rat has not been required, but was found necessary with the CO_2 laser in 16 kg dogs. Ligation of vessels with chromic gut and use of the CO_2 laser were compatable procedures. Since vessel lumens of the human liver are relatively larger than the canine liver more individual ligation of bleeding points per square area will be required. However, in severe liver injury, a generalized ooze frequently persists from capillaries of the hepatic parenchyma in such a fashion that individual suture ligation of bleeding points is not practical and, in fact, ineffective. The great capability for hemocoagulation in the dog required anitcoagulation with heparin to produce a uniformly fatal injury. The heparinized dog model is similar to human liver surgery where coagulopathies are commonly noted because of massive blood loss and replacement. In addition, the human patient is frequently heparinized as part of the technique of transatrial vena caval cannulation when the vena cava is disrupted as part of the liver injury. Uncontrollable parenchymal hemorrhage (from vessels less than 1.5 ml in diameter) is common in these circumstances and this study confirms that the laser is effective in controlling such bleeding.

We feel that partial hepatic lobectomy may now be utilized to resect smaller areas of injury which are currently, simply oversewn leaving behind quantities of necrotic tissue. Larger but still partial hepatic lobectomies may be utilized to replace the anatomic total hepatic lobectomy with decreased operative time and blood loss when conventional and laser methods are permitted to complement one another. It is also recognized that conventional and anatomic total hepatic lobectomy as it is currently practiced will continue to be required in certain extreme clinical situations. The laser is useful in this type of hepatic surgery, however, by controlling persistent parenchymal blood loss. In addition, the laser when used in any of these clinical situations will decrease biliary drainage and residual necrotic tissue thereby reducing the two leading causes of postoperative infection. The time necessary for hepatic surgery will be reduced as well as the quantity of transfusion required. This should have significant effect on reducing postoperative pulmonary complications.

We are currently utilizing the CO_2 laser in controlled operating room situations for primary excision of third degree burns with immediate autografting. To date, the results have been encouraging. We anticipate utilizing the CO_2 laser in the clinical treatment of liver trauma in the near future.

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Carcinoembryonic Antigen and Prognosis in Patients with Colon Cancer

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One-hundred and fifty patients with non-metastatic colo-rectal cancer were followed for a period of 24 to 36 months post-operatively. Preoperative CEA values have been shown to correlate with the extent of the disease and the patient's prognosis. The prognosis for recurrences is greater in patients with elevated pre-operative CEA values regardless of the stage of their disease. This tendency to have recurrences is 1.8 times higher in individuals with increased pre-operative CEA levels. This same relationship occurs to a greater or lesser extent at each stage of the disease.

CARCINOEMBRYONIC ANTIGEN (CEA) was first defined by Gold and Freedman as a tumor specific antigen found in entodermally derived neoplasms of the gastro-intestinal tract.[9,10] Thomson developed a radioimmunoassay to detect CEA in patient's serum.[29] Initial results indicated that this assay method would provide an easy serological test for the diagnosis of colo-rectal neoplasms and stimulated an enormous amount of research in this area. Results of studies by other investigators differed considerably from Thomson's study and indicated that the cancer specificity of CEA was open to question.[7,13,14,17–20,26] It has been well established by several laboratories that a quantitative, rather than a qualitative, difference in CEA exists between normal colon and colonic cancer.[2,3,21,24] Elevated CEA levels have also been found in the sera of patients with a wide variety of benign diseases.[4,14,17,26,28] This lack of tumor specificity has now been documented by Gold's laboratory.[25] It is apparent that the clinical status of the patient be known before interpreting the significance of elevated serum CEA values.

The radioimmunoassay for CEA appears to be of limited value for the primary detection of colo-rectal cancer since many patients with early neoplasms have CEA values in the normal range.[12,14,22,25] Reports from several investigators have shown that only 18–30% of patients with Dukes stage A lesions have increased levels of CEA and that some patients with metastatic disease have normal CEA values.[12,22,25] It has been suggested, however, that CEA determinations may be of value in following patients in the post-operative period to detect recurrences.[30] This study was undertaken to determine if correlation exists between the preoperative CEA level and recurrences after "curative" colon resection.

Materials and Methods

A total of 150 patients with colo-rectal lesions, who had been followed for a period of 24–36 months after initial surgery, were selected. Only those patients who underwent curative resections were included. Those individuals without clinical or laboratory evidence of metastatic disease were staged according to the Dukes classification system. Patients were considered to have recurrences on the basis of clinical, X-ray and laboratory data and not all patients had biopsy proven recurrences. It was not feasible or in the patient's interest to document all recurrences by biopsy.

The CEA levels were determined as previously described.[20,27] The standards were slightly different from those employed by most investigators. Using the current standards provided by Hoffman-LaRoche (Nutley, New Jersey) levels greater than 4.0 nanograms were con-

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TABLE 1

CEA Level (Nanograms/ml)	Dukes Stage* A	B	C
0.0–4.0	21	36	26
4.0–10.0	3	12	13
10.0–20.0	1	9	19
Greater than 20	0	4	6

* Number of patients without known metastasis.

TABLE 3.

Dukes Stage*	Number Dead	% with Increased CEA Levels†
A	3	66%
B	13	30%
C	31	56%

* Without known metastases.
† Greater than 4.0 nanograms using Hoffman-LaRoche standards (2.5 using our previous standards).

sidered elevated. These standards vary somewhat from our standards on earlier studies and our previous published value of 2.5 ng corresponds to 4.0 ng using HLR standards. All plasma CEA determinations were done in the immediate preoperative period. ABO blood group determinations were carried out by our blood bank.

Results

One-hundred and fifty patients with non-metastatic colon carcinoma were followed for a period of 24–36 months after non-palliative colon resection. Forty-four per cent of all patients had elevated levels of CEA during the preoperative period. Elevated levels of CEA were found in 4 of 25 patients with Dukes stage A lesions, 25 of 61 patients with stage B lesions and 39 of 64 patients with stage C disease (Table 1). In general, increased preoperative CEA levels were associated with a poorer prognosis (Table 2). Fifty-seven per cent of those patients who died or were alive with disease had increased CEA values. In comparison, only 32% of those alive and well had elevated CEA values. This association between increased preoperative CEA levels and poorer prognosis extends through all stages of the disease (Table 2). Three of five patients with stage A disease who died or were alive with disease had high plasma CEA values. Of the 20 remaining patients with stage A lesions who were alive and well, only one had a CEA elevation. In patients with stage B disease 53% of those who died or were alive with disease had high plasma CEA values, whereas only 36% of those alive and well had similar CEA elevations. Of 44 patients with stage C disease who died or had recurrences, 70% were associated with increased CEA values compared to 40% of those who were alive and well. The same relationship is seen between prognosis and pre-operative CEA levels if only those who died were considered, except in stage B lesions (Table 3). Sixty-six per cent of patients with stage A lesions and 56% of those with stage C lesions who died had high CEA levels. Only 30% of those with stage B lesions who died had elevated CEA levels. The reason for this is unclear but may be because of the large number alive with recurrences.

Data on blood groups were compiled for all patients studied. There was no correlation of CEA levels with blood type or survival. This data is not charted.

Discussion

The elimination from the series of patients with metastases accounts for the large proportion of patients with stage A and B disease since metastases were most often found in those with Dukes C lesions. Exclusion of patients with metastases also accounts for the low percentage of CEA elevations found in the group as a whole. The correlation between an increased number of CEA elevations with the extent of the disease is in agreement with our previous results and those of others.[12,22,25] The small percentage of positive results in patients with stage A disease has been a consistent finding of several studies and indicates that this assay would be of limited value as a screening procedure. There are several studies, however, that suggest that CEA determinations would be of value in following patients during the postoperative period to detect recurrences.[30]

TABLE 2.

Dukes Stage*	Number of Patients	% with Increased† CEA Values	Number Dead or Alive with Disease	% with Increased† CEA Levels	Number Alive & Well	% with Increased† CEA Levels
A	25	16%	5	60%	20	5%
B	61	41%	19	53%	42	36%
C	64	60%	44	70%	20	40%
All Stages	150	44%	68	57%	82	32%

* Without known metastasis.
† Greater than 4.0 using Hoffman-LaRoche standard. All CEA determinations were done preoperatively.

This study provides evidence that CEA determinations are of value in ascertaining prognosis since recurrences have a tendency to appear in patients with high preoperative CEA values. The chance of developing a recurrence or dying in a three-year period is almost twice as high (1.8:1) in those with elevated preoperative CEA values. It would be tempting to attribute this effect to a specific cell mediated immunological tolerance induced by CEA. This, however, is not supported by several studies which show that CEA has no effect on *in vitro* lymphocyte blastogenesis.[15] CEA could interfere with the humoral antibody response by acting as an antibody sink, as suggested by Gold.[7] Antibodies against CEA have been demonstrated by Gold and other members of his group.[8,11] Attempts by other groups to demonstrate antibodies using Gold's method as well as other investigators' have been unsuccessful.[5,16] Since CEA occurs in normal tissues it is difficult to conceive of autoantibodies being induced in a large percentage of patients without affecting normal tissues. Our current belief, and that of others, is that CEA has little or no effect on the immunological response of the patient.[2]

In view of our findings it seems reasonable to postulate that high CEA levels might be associated with undifferentiated colon carcinomas. Correlation of plasma CEA levels with degree of tumor differentiation have not been carried out but results on tissue studies are available. Martin and Martin could not demonstrate any correlation between tumor differentiation and levels of CEA on the basis of extraction procedures.[23] Recent data based on immunofluorescent studies have shown that the highest levels of CEA appear to be present in well differentiated tumors.[6] These reports are somewhat conflicting and conclusions regarding CEA levels in plasma from patients with varying degrees of tumor differentiation will require further study.

CEA is a glycoprotein and is present on the cell surface. It has been postulated by Apffel and Peters that such a substance may mask tumor specific antigens and therefore protect them from the host's immunologic defenses.[1] Although at present there does not appear to be any clear reason for our findings, we favor their hypothesis. Attempts are under way to elucidate the mechanism involved.

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Management of Umbilical Hernias Associated with Hepatic Cirrhosis and Ascites

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A series of 35 umbilical herniorraphies in patients with cirrhosis of the liver is reported. In this group there were eight significant complications (22%) and six deaths (16%). There was no evidence in this study of increased likelihood of esophageal variceal bleeding secondary to the interruption of portosystemic collaterals in the umbilical region. An aggressive surgical approach is indicated in cirrhotic patients, with umbilical herniae complicated by incarceration, strangulation, rupture, ulceration, and leakage of ascitic fluid. On the other hand it is recommended, that repair of non-complicated umbilical herniae be delayed until the cirrhosis is stabilized, ascites has diminished and nutrition has been improved. In many instances herniorrhaphy may not be necessary after disappearance of ascites.

Umbilical herniorrhaphy in the good risk patient is a relatively simple operation with low morbidity and mortality. Umbilical herniorrhaphy in an advanced cirrhotic presents an operative risk of much greater magnitude and may pose a considerable technical problem when complicated by leakage of ascitic fluid, necrosis of the abdominal wall with ulceration, infection, rupture, or strangulation (Fig. 1). Furthermore interruption of large portal-systemic collateral veins located in the region of the umbilicus may present a challenge to the surgeon and may deprive the patient of an important avenue of portal decompression. Because of the limited number of reports on umbilical herniorraphy in cirrhotic patients and the relative frequency of the problem, it seemed desirable to review 35 patients with cirrhosis of the liver who required umbilical herniorrhaphy in this hospital.

Material and Method

The patients were all males ranging in age from 35 to 76 years with an average age of 53 years. The umbilical hernia had been present for many months (average 15.4 months). The signs of cirrhosis are listed in Table 1. It is noteworthy that 27 (77%) had moderate to massive ascites. The indications for surgery in these patients are shown in Table 2. In some instances there were multiple reasons for surgery, the chief of which is listed in the table. Seven patients required emergency surgery within one to six hours; nine required urgent surgery within 24 hours; and in the remaining 19 patients the procedure was done electively.

Anesthesia was varied; cyclopropane was employed in 11 patients, halothane in six, nitrous oxide in seven, spinal in nine and local anesthesia in two. Anesthesia was administered with care to achieve the minimal depth needed for abdominal relaxation.

Surgical repair consisted of transverse imbrication of fascial layers in 28 patients as originally described by W. J. Mayo.[4] Linear imbrication was used in one patient and transverse approximating closure was used in six patients. The most common technique consisted of a transverse elliptical incision which was made around the umbilicus and hernia encompassing points of perforation and necrotic or inflammed skin. The surface of the anterior fascia was dissected free for a distance of approximately 1½ inches surrounding the hernial sac and defect. The sac was opened, the contents reduced, and the redundant portion of the sac was excised. The peritoneium was closed with a continuous suture of catgut. Interrupted mattress sutures of non-absorbable suture material were then placed through the fascial layer one inch above the margin of the upper flap to the edge of the lower flap in a vest over pants manner. The free edge of the upper flap was then sutured to the surface of the aponeurosis below. Simple interrupted closure of the skin completed the operation (Fig. 2).

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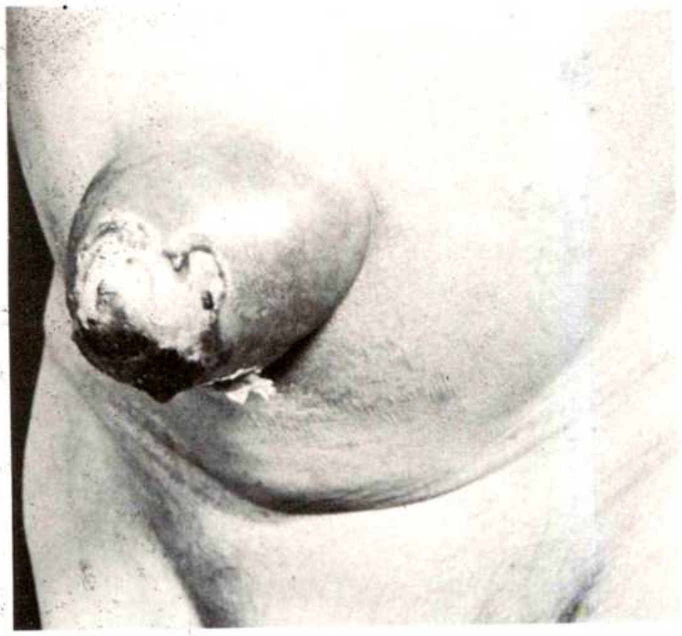

FIG. 1. Preoperative photo of cirrhotic patient with complicated umbilical hernia. Note marked protrusion and ulceration.

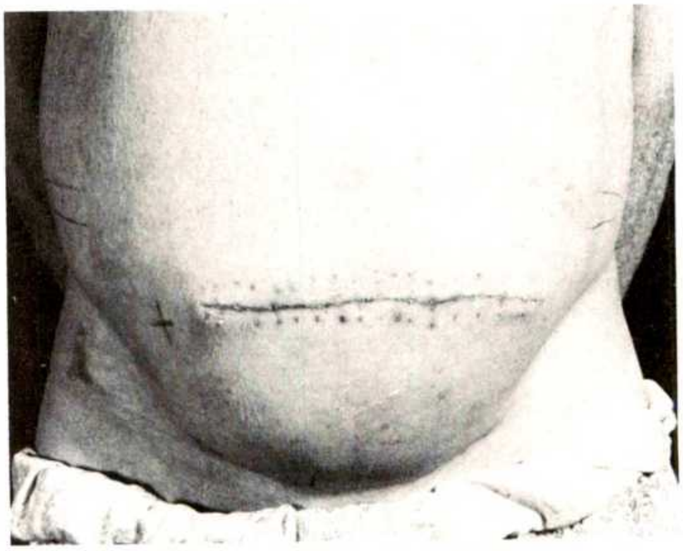

FIG. 2. Postoperative appearance of herniorrhaphy in Fig. 1.

Results

In 27 cases surgery was tolerated well, but in eight cases (23%) there were major complications of which six were fatal. The minor complications (three) consisted of a superficial wound infection, wound seroma, and wound hematoma. All responded to local treatment. Two of the major complications were gastrointestinal hemorrhage occurring two and four weeks following surgery. The first occurred in a patient known to have esophageal varices. The second occurred in a patient with varices who was discharged two weeks postoperatively and returned to the hospital with a bleeding episode one month following herniorrhaphy. In both patients hematemesis was controlled by transfusing one litre of blood. No further treatment was necessary.

TABLE 1. *Signs and Pertinent Laboratory Values in 35 Cases of Cirrhosis*

	Number	Per cent
Hepatomegaly	32	91
Edema	28	80
Ascites	27	77
Vascular spiders	25	71
Collateral abdominal veins	24	69
Esophageal varices	19	54
Splenomegaly	11	31
S. bilirubin > 1.3 mg%	21	60
S. albumin < 3.0 gm%	19	54
Increased Proth. time*	20	57

* Prothrombin time greater than 2 seconds over control values or less than 70% of controls.

TABLE 2. *Indications for Umbilical Herniorrhaphy in 35 Cases*

Spontaneous rupture	3
Leakage	3
Ulcerated skin with impending rupture	7
Incarceration	10
Incarceration with strangulation	3
Abdominal discomfort or pain	9
	35

TABLE 3. *Major Postoperative Complications*

Surgical Indication	Postoperative Course
1. Pain	Hematemesis 2 wks. postop. Recovery after transfusion (1 L)
2. Ulceration	Hematemesis 4 wks. postop. Recovery after transfusion (1 L)
3. Incarceration Leakage	Sudden death in 1 wk. (unexplained)
4. Strangulation	Death in 2 wks. *Staph. peritonitis*
5. Intestinal obstruction	Death in 6 wks. *Staph. peritonitis*
6. Strangulation	Death in 6 wks. *Staph. peritonitis*
7. Ulceration, Impending Rupture	Death in 9 wks. Hepatorenal failure
8. Ulceration, Impending Rupture	Death in 9 wks. Hepatorenal failure

The immediate deaths (six) occurred from one to nine weeks postoperatively (Table 3). Three patients died as a result of staphylococcal peritonitis. These patients were operated on an emergency basis because of intestinal obstruction, two of which had strangulated small bowel requiring resection. Multiple paracentesis was carried out preoperatively in one of these patients because of massive ascites and this resulted in contamination of the ascitic fluid. The second patient required multiple paracente-sis and thoracentesis after operation of massive reaccumulation of fluid. At the time of death the ascitic fluid cultured *staph aureus*, coag. +. The third patient was encephalopathic with signs of hepatic coma prior to operation. The operation was carried out under local anesthesia. The repair was a single layer transverse closure which leaked ascitic fluid and was associated with the development of generalized peritonitis and hepatic coma. The fourth patient had spontaneous rupture of the hernia with extrusion of the omentum. Uneventful repair was followed by sudden unexplained death on the seventh postoperative day. The last two patients were operated upon because of ulceration of the skin with impending rupture. Both died nine weeks following operation from hepatorenal failure.

Discussion

Cirrhosis of the liver predisposes to abdominal hernia, particularly when the disease is complicated by ascites. Chapman, Snell and Rowntree[2,3] observed that in patients with cirrhosis 6 of 58 without ascites had abdominal herniae whereas 47 of 112 patients with ascites had abdominal herniae. Umbilical hernia was the most frequent type, accounting for 24 of the 47 cases.

Umbilical herniorrhaphy in the cirrhotic patient is associated with significant morbidity and mortality. In this series of 35 patients there were six deaths (16%) and eight major complications (22%) in the immediate post operative period. This is in contrast to the report by Yonemoto and Davidson[6] who described a series of nine cirrhotic patients undergoing umbilical herniorrhaphy. Their patients had advanced cirrhosis with ascites. Five had preoperative complications, namely, incarceration in three, strangulation in one, and leakage in one. Except for wound infection in one patient there were no postoperative complications and no deaths. These patients had been hospitalized for months prior to surgery during which time they received optimal nutrition, and their ascites had decreased or disappeared following a low sodium diet. They had been rehabilitated to a considerable degree. In our series 19 patients (54%) were hospitalized less than one month before surgery, and 14 patients for less than one week. In three of six cases with fatal post operative course the period ranged from 1 to 12 days. It seems apparent that the patients described in this report were more vulnerable.

In 1960 Baron[1] reported findings on 16 patients with advanced cirrhosis subjected to umbilical herniorrhaphy. He compared these to a control series of 27 non-cirrhotics with umbilical herniorrhaphy. The single death in the control group was an 83-year-old woman who died from shock postoperatively. In the 16 patients with cirrhosis there were five deaths (31%) all due to bleeding esophageal varices in the immediate postoperative period. (Four died within 11 days and one 24 days after operation). Baron suggested that portosystemic collateral may have been compromised during the operative procedure with a resultant increase in blood flow in the coronary esophageal circuit. Bleeding esophageal varices immediately following herniorrhaphy were not a common feature of our series or the series reported by Yonemoto and Davidson.[6] We are at a loss to explain this high incidence of post herniorrhaphy variceal bleeding in Baron's series.

Spinal or local anesthesia were employed in eight of nine cases described by Yonemoto and Davidson, in 9 of 16 cases reported by Baron, and in 11 of 35 cases in our study. The remainder received chiefly cyclopropane and in a lesser number, halothane. Comparison of the three series reveals no significant differences in patient material, in indications for surgery, anesthesia, or operative procedures. It seems likely that the favorable results reported by Yonemoto and Davidson are attributable chiefly to the long preoperative period which provided time for stabilization of patients with limited hepatic reserves.

Most patients with umbilical hernia secondary to cirrhosis do not require surgery. With subsidence of ascites and with clinical improvement the hernia reduces itself and remains only a flabby tab of tissue.

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Management of Ileal Perforation Due to Typhoid Fever

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The results of the surgical management of 161 cases of ileal perforation due to typhoid fever are presented. Most were seen after an illness of 2–4 weeks, and because of delays in seeking hospital admission, more than half were explored more than 24 hours after their perforation occurred. All patients were prepared for operation with nasogastric suction, intravenous fluids, and antibiotics. At laparotomy, 80% had considerable quantities of pus and small bowel contents in the peritoneal cavity and the remainder had localized abscesses; there were no instances of localization of the perforation. One hundred three of these patients underwent simple closure of their perforations, while 43 underwent small bowel resection, usually because of multiple perforations. Exteriorization or drainage were performed only in patients too sick to tolerate a more appropriate procedure. The overall mortality was 9.9%. The authors believe that typhoid perforations can best be dealt with at operation. Delay in operative intervention adversely affects the survival rate after surgery. Chloramphenicol is used as the drug of choice.

ALTHOUGH uncommon in the United States and Western Europe, typhoid fever remains common in many parts of the Orient. The introduction of chloramphenicol provided effective therapy for typhoid fever, and has markedly lowered the mortality of the disease, as well as the mortality of perforation, which was once thought to be almost universally fatal; it has not altered the incidence of perforation, which remains at about 3%[1,5,11] nor has it eliminated the relapse rate, which may in fact be slightly higher in patients treated with chloramphenicol.

In parts of Asia, typhoid perforation of the ileum is a frequent cause of diffuse peritonitis. Although it continues to account for much of the mortality attributed to typhoid fever, there is still some lingering disagreement over the role of operative intervention in its management. In the early 1960's Huckstep[7] and Woodward[12] argued for medical management; more recently, the consensus has favored operation.[1,3,4–6,9]

Pathogenesis

Typhoid bacilli gain entrance to the body via ingestion of foods or liquids contaminated with infected feces or urine. They are not destroyed by gastric acidity, and reach the blood stream after successfully invading the intestinal mucosa, and traversing the intestinal lymphatics and mesenteric lymph nodes. Bacteremia is established in man several days after the ingestion of viable bacteria and leads to the establishment of secondary areas of inflammation in the liver, biliary tree, spleen, bone marrow, and lymph nodes. From the second week onward, bacteria can be shed from the biliary tree into the upper small bowel, and can appear in the stools. The Peyer's patches undergo swelling and ulceration, which can progress to capillary thrombosis and subsequent necrosis. These ulcerations are always located on the antimesenteric border of the intestine and may perforate or bleed, usually in the third week of the disease, although they usually heal without scar formation. An increase in titer of agglutinins against the somatic (O) and flagellar (H) antigens of S. *typhosa* occurs (the Widal reaction), and usually reaches a peak during the illness.

Clinical Results

One hundred sixty-one patients were seen with typhoid perforation of the ileum on the surgical service of the Seoul National University Hospital between January, 1960 and July, 1973. All were treated by operation. The

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TABLE 1. *Age Distribution of Patients*

Age	Number	Per Cent
0–9	8	5.0%
10–19	20	12.4%
20–29	62	38.6%
30–39	39	24.2%
40–49	19	11.8%
50–59	11	6.8%
60–69	2	1.2%
Total	161	100.0%

TABLE 3. *Admission Temperatures*

Temperature	Number	Per Cent
36 C–37 C	34	21.1%
37 C–38 C	47	29.2%
38 C–39 C	58	36.0%
39 C–40 C	19	11.8%
> 40 C	3	1.9%
Total	161	100.0%

attribution of perforation to typhoid rather than an alternate etiology was made most commonly on the basis of typical clinical and operative findings. Definite serological and bacteriological confirmation was by nature retrospective, and although pursued in nearly all cases, never caused us to delay operation for the 1–3 days required before results became available.

One hundred thirteen patients were male and forty-eight were female, a ratio of 2.4:1. The age distribution of the patients (Table 1) revealed that 63% were between 20 and 39 and 75% were between 20 and 49. There was a definite seasonal prevalence of typhoid perforation reflecting the incidence of typhoid fever, with 64% of cases occurring in either summer or autumn. Most of the patients had been chronically ill with headache, abdominal pain, diarrhea, and myalgia for a variable period of time (Table 2), usually longer than two weeks. Only six patients (3.7%) had been ill for less than one week. Few of these patients had received adequate prior treatment for their illness and almost all sought initial medical attention on an emergency basis because of the sudden and dramatic worsening of their condition caused by acute perforation of the small bowel. Fever was not a striking admission finding, 50% having a temperature of 38 C or less (Table 3). In many, perforation had occurred 24–48 hours prior to hospital admission, and this delay was consequently reflected in the time interval between perforation and operation (Table 4). Thus, only 13.6% of patients were explored within 12 hours, and more than half were explored more than 24 hours after perforation.

At surgery, 80.7% of our patients had generalized peritonitis with varying quantities of small bowel contents and pus in the peritoneal cavity. There was no tendency toward localization or walling-off of the perforation in these patients other than some adherence of the perforated loop of ileum in the pelvis. The remainder had localized abscesses: 8 subphrenic, 5 subhepatic, and 18 pelvic. Eighty-six per cent of the perforations were located within 60 cm of the ileocecal valve, and 72% were within 40 cm (Table 5). Three-quarters were less than 0.6 cm in size, and most were round or ovoid in shape. Thirty-one per cent of our patients had more than one perforation.

Several operative procedures were performed (Table 6). Most patients underwent simple one-layer closure of their perforation with or without debridement, along with appropriate toilette of the peritoneal cavity, while approximately a quarter underwent small bowel resection with primary anastomosis, the indication for this more extensive procedure usually being multiple perforations. Antibiotics were used in all patients. Sixteen patients died, a mortality rate of 9.9%.

Discussion

In endemic areas the diagnosis of typhoid perforation can usually be made without difficulty on the basis of the clinical history extending over a period of 1 to 4 weeks and culminating in the acute picture of enteric perforation. The physical findings are typical of diffuse peritonitis secondary to a perforated viscus, and roentgenologic studies will reveal a pneumoperitoneum in about two-thirds of cases. The differential diagnosis should not be overly difficult. Appendicitis presents a much shorter history and more localized physical findings. Regional enteritis is distinctly uncommon in the Orient, as is colonic diverticulitis; in fact both these entities are common to highly urbanized societies rather

TABLE 2. *Duration of Symptoms Prior to Admission*

Duration	No. Cases	Per Cent
<1 wk.	6	3.7
1–2 wk.	34	21.1
2–3 wk.	74	46.0
3–4 wk.	30	18.6
4–6 wk.	14	8.7
>6 wk.	3	1.9
Total	161	100.0

TABLE 4. *Duration of Perforation Prior to Operation*

Time	Number	Per Cent
<6 hr	7	4.3%
6–12 hr	15	9.3%
12–24 hr	47	29.2%
24–48 hr	46	28.6%
48–72 hr	24	14.9%
72–96 hr	5	3.1%
>96 hr	17	10.6%
Total	161	100.0%
Mean (hr.)	38.4	

than those where typhoid fever is prevalent. Perforation due to ascaris is a dubious diagnosis, as these roundworms do not possess teeth and are thought incapable of penetrating the intact bowel wall. As serologic and bacteriologic conformation requires a delay of one to three days before therapy is instituted, our policy has been to begin vigorous resuscitation with intravenous fluids, nasogastric suction, and antibiotics, and proceed to exploratory laparotomy, utilizing bacteriologic studies as a *post facto* aid to subsequent management rather than as an argument for operative intervention. Moreover, as pointed out by Huckstep,[12] the Widal test may be negative in patients with typhoid, the blood may be sterilized within hours of the administration of chloramphenicol, and stool culture may not be positive until the third week of the illness. In our experience Widal titers were more useful in confirming the diagnosis of typhoid than either blood or stool cultures, as might be predicted by the fact that bacteremia and shedding of typhoid bacilli are sporadic even before the institution of antibiotics. Moreover, many of these patients had received antibiotics on a casual basis from local practitioners, usually as therapy for one or another of their symptoms. Titers of 1:80 or greater were seen in 75% of patients tested. Occasionally, titers may be low even in the presence of obvious typhoid fever, particularly early in the disease. We have observed several patients with low titers early in the disease who grew out *S. typhosa* from either stool or blood.

At surgery, there was no instance where sealing or walling off of the perforation had occurred, and 80% of the patients had large quantities of small bowel contents and pus in the peritoneal cavity, two observations that made us increasingly skeptical of the possible efficacy of nonoperative treatment. Moreover, in Orientals the greater omentum is frequently minimally developed, further mitigating against any possible natural "localization." Other authors were nearly unanimous in failing to observe instances of walling off among typhoid perforations.[1,5] In addition, the paralytic ileus occurring with peritonitis of this magnitude ensures a continuing discharge of small bowel contents into the peritoneal cavity from the dilated proximal small bowel. The opportunity to remove this material as well as the opportunity to deal with the continuing source of contamination by suture or resection seem incontrovertible benefits of surgical intervention.

TABLE 5. *Operative Findings*

Distance of Perforation from Ileocecal valve	Number of Patients	Per Cent
0–19 cm	52	32.3
20–39 cm	64	39.7
40–59 cm	22	13.7
60–79 cm	8	5.0
80–99 cm	12	7.5
>100 cm	3	1.8
	161	100
Number of Perforations		
1	111	68.9
2	30	18.6
3	15	9.3
4	4	2.5
5	1	0.7
	161	100

TABLE 6. *Operative Procedures in Typhoid Perforation*

Procedure	Operations	Deaths	Mortality Rate
Primary closure	103	11	10.2%
Resection and anastomosis	43	3	7%
Ileostomy	10	1	10%
Drainage	5	1	20%
Total	161	16	9.9%

The operative procedure performed depended on the surgeon's preference, but was usually simple one-layer closure of the perforation, with or without debridement, and extensive toilette or the peritoneal cavity. Resection and primary anastomosis were usually performed because of multiple perforations, and ileostomy or simple drainage were performed only in the most critically ill and moribund patients.

The operative procedures performed, and their mortality rates are seen in Table 6. There seemed to be little relation between the type of procedure performed and the complication rate, except that patients undergoing resection and anastomosis had a slightly lower rate of pulmonary complications and patients undergoing ileostomy had a lower incidence of wound problems and a higher incidence of prolonged ileus.

The mortality rate of the entire series was 9.9%, and is compared with other recent series in the literature (Table 7). As might be expected, the mortality and complication rates were directly related to the time elapsed between the onset of peritonitis and hospitalization, as noted previously by others.[2,4]

The forty-three patients undergoing resection enjoyed a slightly lower mortality rate than those undergoing simple closure, in spite of the more extensive disease usually found in the former group. Because of this finding, we have been less hesitant to perform a small bowel resec-

TABLE 7. *Studies of Typhoid Perforation Treated by Operation*

Author	Country	Year	Cases	Mortality
Conroy	Korea	1957	50	22%
Li	Hong Kong	1963	20	10%
Dickson	Nigeria	1964	38	58%
Carayon	French West Africa	1965	98	28%
Dawson	Korea	1970	213	13%
Le Peltier	Morrocco	1971	26	46%

tion in recent years if it seemed indicated. In so doing, we have attempted to remove as little distal ileum as the pathology would allow, and have attempted to preserve the last few centimeters of ileum along with the ileocecal valve, since this area was usually not involved. Others[8] have reported similar success with resection and primary anastomosis: Carayon[3] reported seven resections without a death in a series that had an overall mortality of 28%, and Conroy[4] performed resection perferentially with an acceptable mortality rate amid the sub-optimal conditions of a military hospital.

We have continued to utilize chloromphenicol as the drug of choice in typhoid fever. It is initially given intravenously, then continued by the oral route for a total of 12 to 14 days after oral feedings are resumed. Recently, Ampicillin has been increasingly popular in the United States for this disease but its therapeutic effect is not as rapid or as predictable, and it is less available and more costly than chloramphenicol in most parts of the world. We believe that chloramphenicol remains superior in instances of acute bowel perforation of presumed, but not proven, typhoid etiology. We have encountered no instances of aplastic anemia in our series, and Huckstep[7] and others with a larger experience have been likewise fortunate. When chloramphenicol has been unavailable, or the diagnosis less clearcut, we have used kanamycin. Our attempts to culture the peritoneal fluid, and those of others have yielded an overwhelming percentage of cultures positive for *E. coli* and only a few instances where S. *typhosa* grew out, suggesting that perhaps the treatment of typhoid fever and the treatment of perforated small bowel might each require a different chemotherapeutic rationale in a given patient. We have utilized steroids only for the treatment of septic shock, and then in appropriately high doses.

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Traumatic Injuries to the Duodenum:

A Report of 98 Patients

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Data of 98 patients who had sustained traumatic injuries to the duodenum during a recent 7-year period is reviewed. The overall mortality was 23.5%; that of the blunt injury group was 35%, that of the penetrating injury group was 20%. However, after the establishment of a trauma unit, the mortality for duodenal injuries fell from 32% to 12%. Death from duodenal wounds may be reduced by earlier hospitalization, earlier diagnosis and consequently earlier surgical repair. Vigorous treatment of shock is essential. A specialized trauma unit with personnel experienced in the management of shock and trauma problems provides a better environment to carry out the preoperative and postoperative care of the acutely injured patient. Adequate surgical treatment of the blunt injury and missile injury of the duodenum should consist of the following procedures: 1) repair of the duodenal wall utilizing conventional techniques; 2) internal decompression of the repair by afferent jejunostomy; 3) efferent jejunostomy for postoperative feeding; 4) temporary gastrostomy; and 5) external drainage of the repair. In certain selected instances, the simple stab wound of the duodenum may be treated by conventional repair without decompression, but a loop of jujunum should be sutured over the repair to prevent delayed disruption. The majority of patients with injuries to the duodenum have associated organs injured which also require considered surgical judgment and action.

Successful surgical repair of a duodenal rupture was first reported in 1896,[13] but it was not until 1905 that the first detailed case report of a survival appeared. Since this time, the number of patients with duodenal injuries increased markedly[4,6] largely because of increased numbers of automobile accidents.[1,3] and the increased violence on our streets.[17] Thus, physicians treating civilian trauma are being confronted with increasing numbers of duodenal injuries.[4,21,24] But reappraisal of all aspects of duodenal injuries is necessary, if the tragically high morbidity and mortality is to be lowered.

Surgical management of duodenal injuries as presented in the literature is controversial, if not somewhat contradictory.[3,16,21] The experience of most surgeons in this disorder is still limited by its relative infrequency. The surgical literature on duodenal injuries mostly consists of isolated case reports or collective reviews of small series and few authors have had sufficient experience with this injury to develop comprehensive analyses of the problem.[4,6,16,23] Furthermore, many reported series include patients treated by highly variable surgical techniques during the early part of the twentieth century when principles of pre- and postoperative care were poorly developed.

The present study presents data of 98 surgically treated traumatic injuries of the duodenum in order to redefine the concepts of resuscitation, diagnosis, and treatment.

Clinical Data

Type of Injury

From January 1962 through December 1968, 98 patients (or 0.03% of all those hospitalized) were operated for traumatic injuries of the duodenum. There were 75 penetrating injuries, of which 51 resulted from small caliber gun shot wounds and 24 from stab wounds as well as 23 nonpenetrating abdominal injuries. The latter included 12 blunt injuries from automobile accidents, five patients

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who were beaten, four patients who fell from various heights and two patients who were kicked and stomped upon. The overall mortality was 23.5% (Table 1).

Sex and Age

The series included 86 males and 12 females who ranged in age from six to 52 years (average 29 years) (Table 2). The majority were between 20 and 40 years (Table 3). The average age of the patients who died was 33 years.

Admission Findings

Twenty-four of this series were admitted in shock; of these, four incurred blunt injury, 14 gunshot wounds and six were stabbed. Thirteen (54%) of these were refractory to the usual preoperative resuscitative measures and required emergency surgery as part of their resuscitation; 12 subsequently died. No male patient complained of testicular pain and none had soft tissue emphysema. Thirteen of 19 adult patients with blunt abdominal injury were intoxicated at the time of their injury. Most of these did not seek medical care immediately following their accident, but waited until they were sober; then, they were unable to remember, or failed to give an accurate account of an accident. Lack of an accurate history often misled the examining physician into incorrect diagnoses. Consequently, many patients had prolonged delays in the preoperative period which may have contributed to increased morbidity and mortality.

X-Ray Findings

Seven of 17 patients with ruptures of the duodenum from non-penetrating trauma had x-ray findings compatible with intraperitoneal organ injury; 3 of these had free intraperitoneal gas. In 12 patients with penetrating trauma, free gas or retroperitoneal gas was demonstrated on scout films of the abdomen.

A correct preoperative diagnosis of intramural hematoma of the duodenum was made in four patients that had incurred blunt abdominal trauma; the diagnosis was based upon radiographic findings of the preoperative upper gastrointestinal contrast study.[10,14]

TABLE 1. *Type of Injury and Mortality of 98 Duodenal Injuries*

Type of Injury	Number of Patients	Deaths	Mortality
Penetrating Injuries	75	15	20%
Stab Wounds	24	2	
Gunshot Wounds	51	13	
Blunt Injuries	23	8	35%
Falls	4	2	
Blows	5	1	
Kicked	2	0	
Automobile Accidents			
Pedestrians	3	2	
Drivers	9	3	
Total	98	23	23.5

TABLE 2. *Sex and Average Age of Patients With Duodenal Injuries*

Type of Injury	Sex Male	Sex Female	Average Age (Years)
Stab Wounds	23	1	32
Gunshot Wounds	44	7	27
Blunt Injuries	19	4	31
Mean			29

Preoperative Management

Patients with nonpenetrating abdominal trauma present much greater diagnostic challenges than do penetrating injuries. The clinical manifestations of blunt abdominal trauma may be unimpressive early in the post-injury period; evidence of this lesion usually becomes apparent to the surgeon only when pathophysiologic derangements take place. Because they produce a paucity of signs and symptoms, retroperitoneal duodenal injuries tax the diagnostic capabilities of the most astute surgeon; early recognition and operative treatment of duodenal injuries is the exception rather than the rule. Rather than relying solely on physical findings to establish a diagnosis, the surgeon should make use of various diagnostic aids, such as abdominal films, gastrointestinal contrast studies, abdominal paracentesis and serum amylase measurements.

The majority of gunshot wound patients were operated as soon as their respiratory and circulatory function was stabilized by appropriate measurements. Seven gunshot patients, despite massive infusions of blood and colloid, remained in extreme shock prior to surgery. These patients were taken to surgery in shock to arrest massive intraabdominal hemorrhage; the emergency surgery was considered an integral part of therapy.[18,19]

Operative Findings

There were 49 injuries to the second portion of the duodenum, which was the most frequently injured part. The first portion was injured 5 times, the third portion

TABLE 3. *Mortality of All Patients With Duodenal Injuries in Relation to Age*

Age in Years	Number of Patients Total	Number of Patients Deaths
Under 9	2	1
10–19	19	2
20–29	33	4
30–39	24	7
40–49	18	8
50–59	2	1
Total	98	23

16 times and the fourth portion 13 times. Fifteen patients had more than one portion injured. The combined injuries were often the result of multiple injuries.

Six patients who incurred blunt injuries had complete transection of the injured duodenum; seven others had over 50% of their duodenal wall circumference transected; and two patients had less than 50% of their duodenal wall circumference injured. Eight additional blunt injury patients had intramural hematomas of the duodenum; two of these had coexisting perforations.

All but two of the gunshot wounds penetrated the duodenal wall in two places; i.e., they were through-and-through injuries. Many of the gunshot wounds produced large duodenal wall defects; however, the duodenum was never completely transected by a missile. Of 24 stab wounds, 17 were through-and-through injuries.

Surgical Treatment

All penetrating wounds of the duodenal wall were treated by debridement of the site of perforation and closure of the defect with either two or three layers of inverting sutures. The inner layers were closed with chromic catgut and the outer layer with silk. All sutures were placed with care to prevent compromise of the duodenal lumen; the majority of the wounds were closed in a transverse diameter.

Eight of 15 duodenal wall perforations or partial disruptions secondary to nonpenetrating trauma were debrided and closed. Five patients with complete transections of the duodenum had debridement of the wound edges and end-to-end anastomoses. One patient had the second, third and fourth portion of the duodenum resected and the gastrointestinal tract continuity reestablished by gastrojejunostomy; the pancreatic and biliary drainage was restored with a roux-en-Y loop. Another patient with blunt abdominal injury underwent partial gastric resection with gastrojejunostomy for duodenal bulb injury. The eight patients with intramural hematomas were treated by drainage of the hematoma into the lumen and bypass of the duodenum by gastrojejunostomy or various other procedures.

Various ancillary procedures were used as adjuncts to the primary duodenal repair. These producers can be divided into two categories: 1) repair of the duodenum with or without external drainage and 2) repair of the duodenum, decompression of the repair, and external drainage. Decompression of the repair was accomplished by either diverting the gastric secretions through a gastrojejunostomy or gastrostomy and jejunostomy with passage of a soft rubber catheter through the proximal jejunum to the region of repair: this will be referred to as an "afferent" jejunostomy tube. Other surgical adjuncts used in both categories include feeding jejunostomy (or "efferent" jejunostomy), gastrojejunostomy and omental or jejunal patch, as a reinforcement of the duodenal repair.

There were 53 patients in the first category (repair with or without external drainage) who had 30% mortality (Table 4). Six surviving and eight nonsurviving patients in this group had complications, which included either duodenal fistula or gastrointestinal tract bleeding. Of the five patients with stab wounds in this group, none had injured more than one wall of the duodenum, none had external drainage and only two had injury to other organs.

The second therapeutic category included 39 patients who had some form of decompression of the duodenal repair. There were 12 blunt injuries, seven stab wounds and 20 gunshot wounds in this category. Only six (15%) of the patients in this group died; all of these deaths were among the 25 patients treated by primary repair of the duodenum, gastrojejunostomy and external drainage of the repair. Five living and one dying patient among the 25 treated by gastrojejunostomy developed either a duodenal fistula or gastrointestinal tract bleeding. Fourteen patients (4 stab wounds and 10 gunshot wounds) in this therapeutic category were treated by internal decompression of the repair. This was accomplished by passing a soft rubber catheter through the proximal jejunum to the region of repair and applying gentle suction postoperatively. These patients also had an efferent jejunostomy, gastrostomy and external drainage. All 14 of these patients survived and none developed duodenal complications or gastrointestinal bleeding.

External drainage of the area of duodenal repair was accomplished with multiple Penrose drains through

TABLE 4. *Surgical Management of 92 Patients With Traumatic Perforations of the Duodenum*

Surgical Procedure	Number of Patients	Deaths	Complications: Living Patients	Complications: Dying Patients
Repair Group	53	16	6	8
Repair only	5	0	1	0
Repair and Drainage	31	11	2	6
Repair, Drainage and Gastrostomy	9	3	2	1
Repair, Drainage, Patch with Jejunum or Omentum	8	2	1	1
Repair and Decompression Group	39	6	5	1
Repair Duodenum, Drainage, Afferent and Efferent Jejunostomy and Gastrostomy	14	0	[illegible]	0
Repair, Drainage and Gastrojejunostomy	14	2	4	0
Repair, Drainage Gastrojejunostomy and Gastrostomy	11	4	1	1

lateral stab wounds in 52 patients; 29 other patients had a combination of multiple Penrose drains, and sump or Chaffin-Pratt drainage. The pancreas, liver and gall bladder, when injured, were also drained and repaired.

Associated Injuries

Associated injury to adjacent organs commonly accompanied duodenal injury. Data of 206 associated abdominal injuries in 88 patients are summarized in Table 5. The pancreas was the most frequent associated organ injured; this was followed by liver, stomach, small bowel, vena cava, genito-urinary system, extra-hepatic biliary system, major arteries, etc. Extra-abdominal injuries also accompanied duodenal trauma, especially in the patient with multiple blunt injury and multiple gunshot wounds. Three of the blunt injury patients had concomitant chest injuries including multiple fractured ribs, hemothorax and pneumothorax.

Delay in Treatment

The majority of our patients were transported from the scene of the accident to other hospital emergency rooms, doctors' offices or other first aid areas. Often after considerable delay, the patient was transferred for definitive surgical care. Many of the transferred patients arrived in shock, frequently with either inadequate or no attempts at resuscitation. This prior, but often inadequate, medical therapy was reflected in the increased mortality (Table 6). Thus, 62 patients receiving prior medical therapy had a mortality rate of 27%. In contrast, the mortality for 36 patients brought directly to the institution was 17%.

Prior medical therapy often contributed to delays in the surgery. We have noted a direct relationship between mortality and the time interval from injury to surgery. Those patients who survived were found to have been operated upon three times as early as those patients who subsequently died. However, even in surviving patients, the time interval from injury to surgery was unduly long and should have been reduced.

TABLE 5. *Associated Intra-Abdominal Injuries in 88 Patients*

Type of Injury No. of Cases	Gunshot 51	Stab 20	Blunt 17	Total 88
Organ Injured				
Pancreas	18	10	9	37
Liver	23	6	3	32
Colon	18	4	2	24
Stomach	18	2		20
Small Bowel	15	3	1	19
Vena Cava	14	4	1	19
Genito-urinary	10	33	1	14
Extra-hepatic	10	2	1	13
Major arterial	10	3		13
Retroperitoneum	1	2	2	5
Spleen	2	1	1	4
Diaphragm	1	2	1	4
Aorta	2			2
Total	142	42	22	206

TABLE 6. *The Relationship of Previous Medical Treatment to Mortality*

	No Previous Treatment		Previous Treatment	
Type of Injury	Number	Died	Number	Died
Stab Wounds	12	2	12	0
Gunshot Wounds	19	3	32	10
Blunt Injuries	5	1	18	7
Total	36	6 (18%)	62	17 (27%)

Effect of Specialized Facilities for Treatment of Trauma Victims

Initially, injured patients were admitted to the general surgical services, but about midway through this study a trauma and shock unit was established to provide specialized care for trauma patients. Forty-one patients with duodenal injuries were cared for on this unit; 5 or 12% died. By contrast, during the 4 years preceding the establishment of the trauma unit 18 of 57 patients with duodenal injuries (32%) died. Only 3 deaths occurred in the group of 26 gun shot wound patients treated on the trauma unit, in contrast to 10 deaths among 25 patients treated for missile injuries before the trauma unit. The patients treated in the trauma unit sustained more severe injuries; the majority of the 23 surviving gun shot wound patients from the trauma unit group had multiple associated organ injuries, including 10 vena cava and 11 hepatic injuries. Moreover, patients treated on the trauma unit had an average of 2.8 associated organs injured, compared to only 1.7 associated organ injuries among the missile injury patients treated before the trauma unit was initiated.

Complications and Mortality

There were 85 postoperative complications in 43 surviving patients and 43 complications in 19 patients who died (Table 9). Infection was the commonest complication; it accounted for 34% of nonfatal complications and for 28% of the complications in fatal cases. Pulmonary

TABLE 7. *Relationship of Time Interval From Injury to Surgery*

	All Patients		Living Patients		Dying Patients	
Type of Injury	Cases	Hours	Cases	Hours	Cases	Hours
Stab Wounds	24	6.2	22	6.5	2	4
Gunshot Wounds	51	7.3	38	5.3	13	18.3
Blunt Injuries	23	115.4	15	86.6	8	169.2
Total	98	35.1	75	21.8	23	71.7

TABLE 8. *Relationship of the Trauma Unit to Mortality From Duodenal Injuries*

Type of Injury	Before Trauma Unit Number	Before Trauma Unit Deaths	Before Trauma Unit Percentage	In Trauma Unit Number	In Trauma Unit Deaths	In Trauma Unit Percentage
Stab Wounds	14	1	7%	10	1	10%
Gunshot Wounds	25	10	40%	26	3	12%
Blunt Injuries	18	7	39%	5	1	20%
Total	57	18	32%	41	5	12%

complications accounted for 32% of nonfatal complications and 21% of the complications in dying patients.

Of the complications specific for duodenal injuries, duodenal fistula was observed in 10 patients, 4 of whom died. Five surviving and five nonsurviving patients had postoperative gastrointestinal bleeding. Data of other postoperative complications are detailed in Table 9.

Twenty-six patients underwent one or more additional operations to correct postoperative complications or to reestablish gastrointestinal tract continuity (Table 10); nine of these patients died. The secondary operations included 13 operations to drain various infections and 11 operations to control gastrointestinal or intra-abdominal bleeding. Nonfunctioning gastrojejunostomies were revised in four patients. Six patients had colostomies performed at their initial operation; these colostomies subsequently were closed. One patient underwent closure of a duodenal fistula and another patient was operated on to correct a pancreatic fistula.

Four patients who did not recover from severe shock expired during the first 24 hours following surgery. Their shock state was not altered by massive infusions of electrolyte solutions, plasma, colloid and whole blood. Each of these patients had multiple associated injuries that materially contributed to their fatal outcome.

TABLE 9. *Postoperative Complications*

Complication	Living Patients (43)	Dying Patients (19)
Infection		
Wound Infection	19	5
Intra-peritoneal Abcess	9	4
Septicemia	1	3
Pulmonary		
Bronchopneumonia	15	8
Atelectasis	8	1
Pleural Effusion	4	
Hemorrhage		
Gastrointestinal	5	5
Intra-abdominal	1	4
Gastrointestinal		
Duodenal Fistula	6	4
Pancreatic Fistula	6	1
Anastomatic Obstruction	2	2
Biliary Tract Fistula	3	1
Renal		
Anuria		3
Neurological		
Delerium Tremens	6	2
Total	85	43

Discussion

During the past 25 years, the routine use of whole blood transfusions, antibiotic therapy, a better understanding of fluid and electrolyte replacement, improved anesthesia and earlier surgical exploration have failed to lower appreciably the morbidity and mortality of traumatic duodenal injuries. We believe that certain modifications and refinements in operative technique and improvements in pre- and postoperative care can reduce the previous excessive morbidity and mortality from traumatic duodenal injuries to more acceptable levels.

There is considerable controversy about the optimal treatment of the injured duodenum in the medical literature. Various authors have proposed a spectrum of therapy from simple closure[7,26] on the one extreme to resection of the injured duodenum[3] on the other extreme. The majority of authors advocate additional surgical procedures to defunctionalize the duodenum, in order to protect and insure the integrity of the repair.[21] The latter procedures include: 1) diversion of the gastric secretions from the repair as in gastrojejunostomy,[24] duodenojejunostomy,[6,15] and duodenostomy;[9,16] 2) internal decompression of the repair as in afferent jejunostomy;[21] 3) exclusion of gastric secretions as in pyloric closure;[22] 4) removal of gastric secretions by gastrostomy;[5] and

TABLE 10. *Summary of Secondary Operations*

Operation	Living Patients (17)	Dying Patients (9)
Drainage of Abscesses		
Subphrenic	5	3
Pelvic	2	1
Intra-abdominal	1	
Subdiaphragmatic	1	
Control of Bleeding		
Gastrointestinal	3	5
Intra-abdominal	1	2
Revision of Gastro Jejunostomy	2	2
Closure of Fistula		
Duodenal	1	
Pancreatic	1	
Closure of Colostomy	6	
Total	23	13

5) inhibition of gastric secretions by antrectomy and vagotomy.[9]

The morbidity and mortality of the present series indicate that some form of internal decompression of the repair should be an integral part of the surgical treatment of traumatic perforations of the duodenum. This decompression may be accomplished by gastrojejunostomy or by jejunostomy which permits suction in the early postoperative period. An "afferent" jejunostomy tube for internal decompression provides the means for reducing the hydrostatic pressure normally present within the duodenal lumen.[2] This hydrostatic pressure arises from the large volume of biliary, duodenal, gastric and pancreatic secretions normally passing through the duodenum. Edema of the duodenal wall at the site of surgical repair, collection of fluid within the duodenal lumen, and decreased peristaltic acitvity follow injury and repair. These factors increase both the volume of fluid within the lumen and the duodenal emptying time. The increased hydrostatic pressure that results may be great enough to disrupt mechanically the repair. Use of internal decompression tends to prevent accumulation of fluid that may lead to a failure of the repair.

Ten patients in our series developed a duodenal fistula, and 4 of these patients died as a direct result of the fistula. Duodenal fistula, which is a most distressing postoperative complication may lead to uncontrolled loss of duodenal contents, starvation, severe wasting, cachexia, and fluid-electrolyte problems including metabolic alkalosis, dehydration, hyponatremia and hypokalemia.

Some authors advocate jejunostomy tubes for treatment of a duodenal fistula.[8,25] By inserting a jejunostomy tube at the time of primary repair, the surgeon may discourage fistula formation. If a duodenal fistula develops, the previously inserted jejunostomy tube provides an immediate means of treatment without resorting to subsequent surgical procedure.

The repair may also be decompressed by gastrojejunostomy. However, the patient may develop a marginal ulcer, if truncal vagotomy is not performed at the same time.[3,15] Four of our patients treated by gastrojejunostomy without truncal vagotomy developed marginal ulcers; two of these patients later bled massively and required emergency surgery.

The majority of patients with traumatic injuries of the duodenum are extremely ill when brought to surgery; frequently they have serious associated injuries that also require surgical correction. Any procedure that reduces the magnitude of operation or decreases the operating time is highly advantageous. The placement of two jejunal tubes and a gastrostomy may be accomplished rapidly as compared with the added operating time necessary to perform truncal vagotomy and gastrojejunostomy. When the "three tubes" (afferent jejunostomy for decompression, efferent jejunostomy for feeding, and gastrostomy for decompression proximal to duodenal repair) are used, the possibility of the patient later developing fistula or marginal ulcer is minimized.

A temporary gastrostomy is constructed to insure adequate gastric aspiration and decompression proximal to the duodenal closure. Many patients with duodenal injuries require prolonged gastric decompression; temporary gastrostomy eliminates the need for extended nasal intubation which often leads to respiratory and gastrointestinal complications.[12,20]

Simple repair without decompression may be adequate for small stab wounds of the first or second portion of the duodenum, especially when there are no associated abdominal injuries. Five stab wound patients of the present series had simple repair of a single injury, but one of these patients developed a duodenal fistula. If the surgeon elects only to repair the small stab wound, the fixation of a loop of jejunum over the repair may be indicated.[7]

Delay in diagnosis and consequent delay in surgical intervention were two factors that contributed to unsatisfactory results, especially in patients with blunt injury. Delayed diagnosis results from delayed hospitalization, inadequate history, especially in the inebriated patient, prolonged hospital observation, lack of initial symptoms or physical signs referable to the duodenum and failure to suspect this disorder on the part of the attending surgeon. In the present series, the surviving patients were operated on much sooner than those who subsequently died. This is in disagreement with Cocke and Meyer[7] who found that the number of hours from injury to operation apparently had no bearing on morbidity or mortality rates. Patients that were brought directly to the hospital had a much lower mortality than those patients treated for variable periods of time elsewhere and then transferred.

Twelve of 24 patients admitted in shock expired. Nine patients were admitted to the trauma unit in shock; four of these patients died. An additional 5 patients went into shock after being hospitalized; however, none of these patients were treated on the trauma unit. Aggressive management and prevention of shock were considered essential in the preoperative management of these patients. Further reductions in the mortality associated with duodenal injuries may come through improvement in the therapy of shock; trauma centers may provide the highly specialized care necessary to treat optimally the injured patient who is in shock and to prevent shock from occurring.[18,19]

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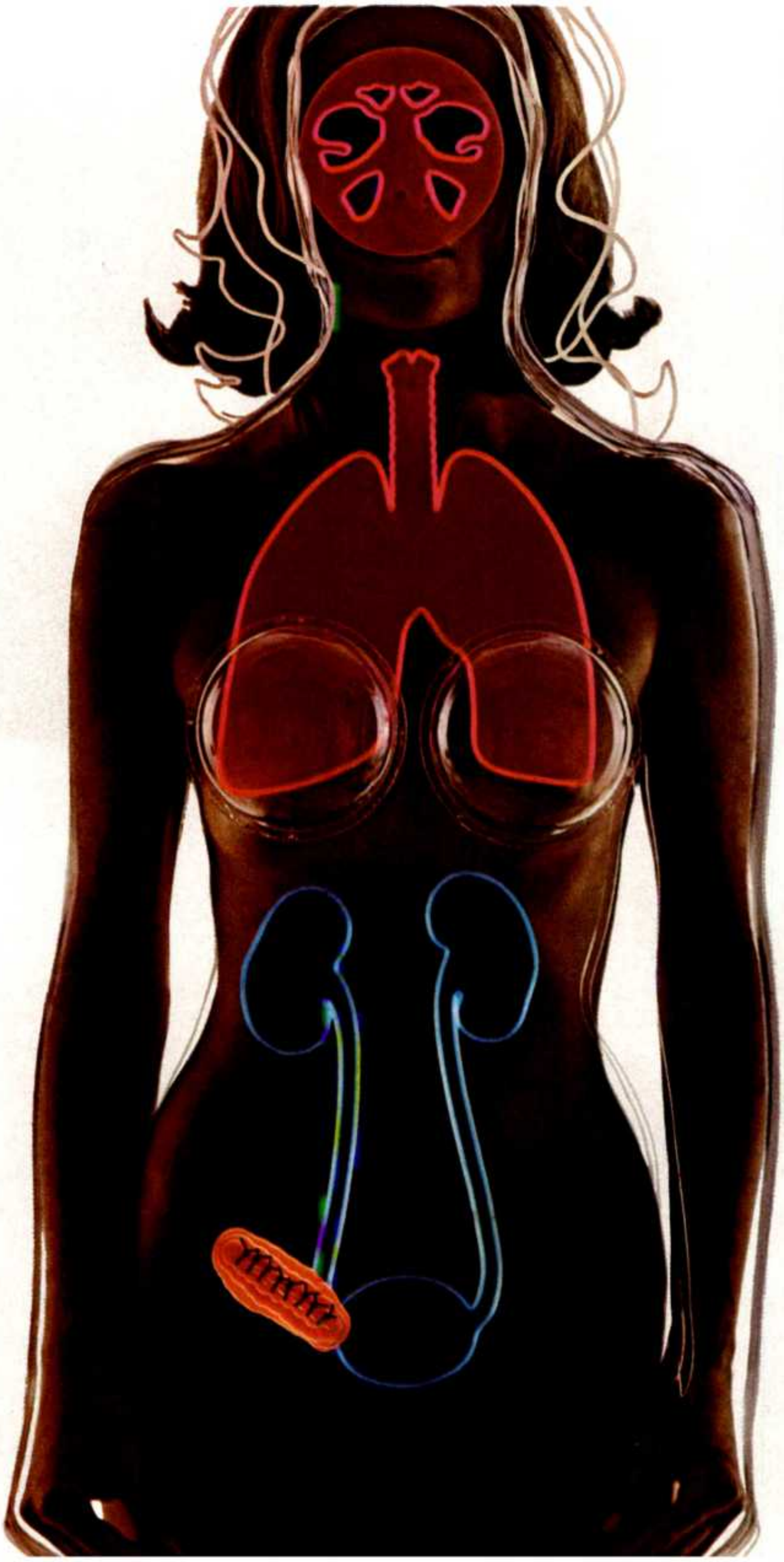

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- Excreted essentially unchanged in the urine.
- Acid stable. Can be given without regard to meals.

'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. **In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.**

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

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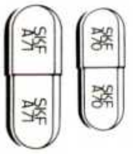

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephradine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella sp.
Hemophilus influenzae

Note—Some strains of enterococci (*Streptococcus faecalis*) are resistant to cephradine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris.* It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated micro-organisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae.*

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae. Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli, Pr. mirabilis,* and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Anspor (cephradine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See *DOSAGE AND ADMINISTRATION* section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest® tablets, but not with enzyme-based tests such as Clinistix® and Tes-Tape®.

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephradine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae,* doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

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ANSPOR (cephradine, SK&F) Capsules—250 and 500 mg.

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cerebral

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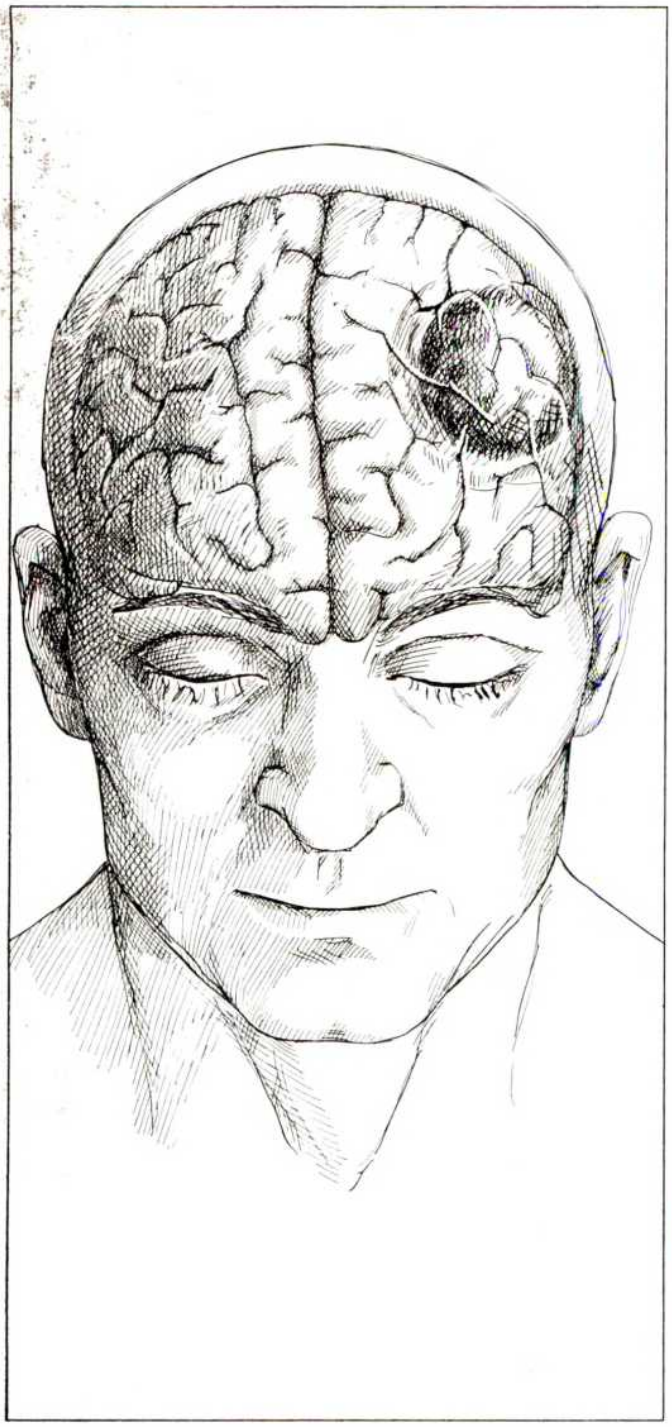
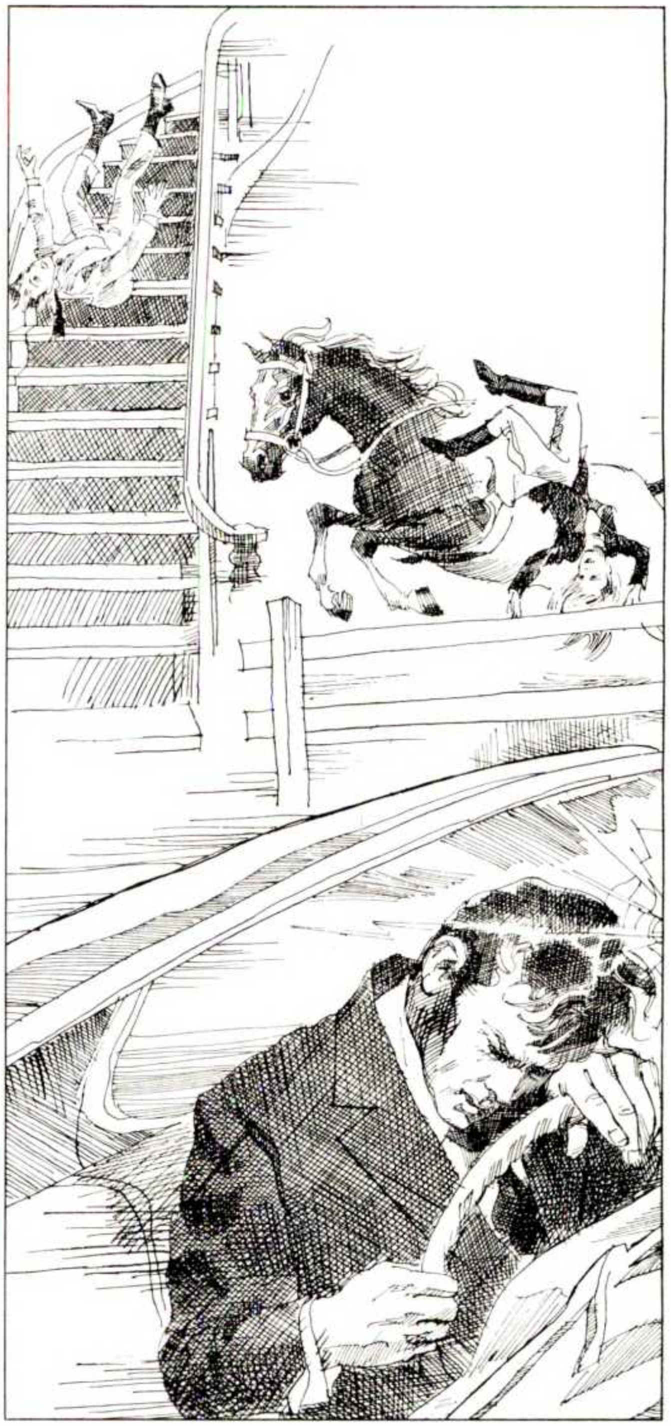


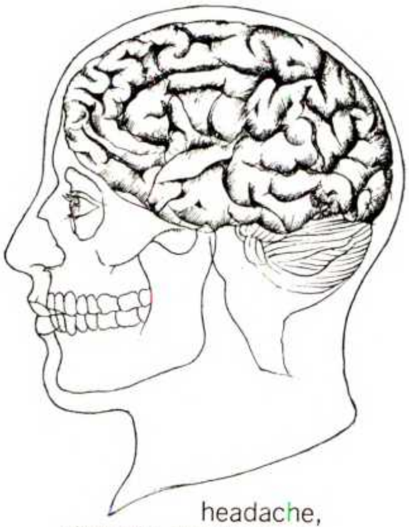
expect it in the presence of severe head injury.



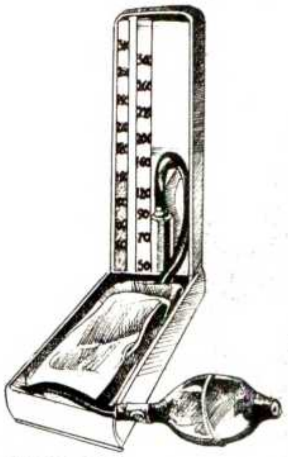
edema*

suspect it in the presence of signs and symptoms such as these:

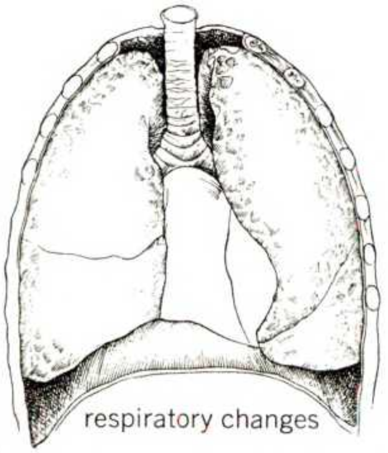
projectile vomiting



headache, altered consciousness



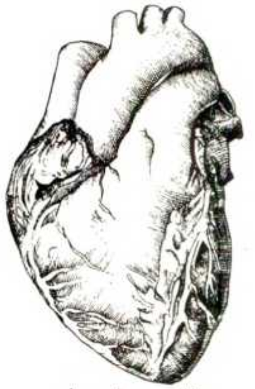
increased blood pressure



respiratory changes

dilated pupil, papilledema,

unilateral or bilateral abducens palsy



bradycardia

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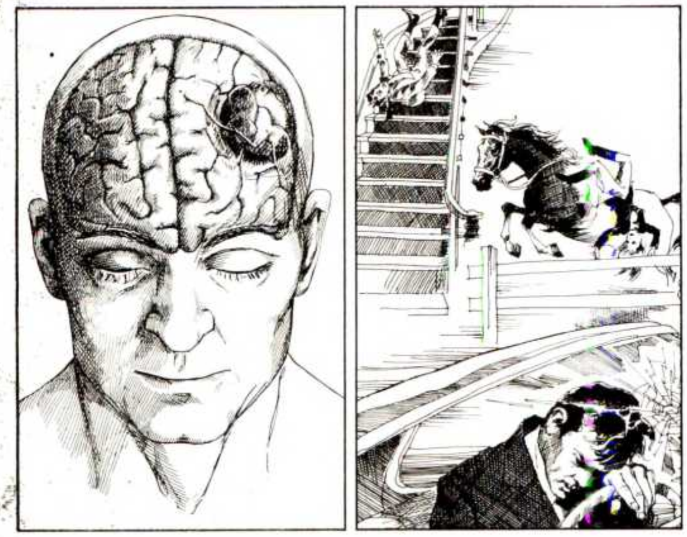

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Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

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Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction; hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

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Physiologic Effects of Hyperventilation and Phlebotomy in Baboons:

Systemic and Cerebral Oxygen Extraction

C. R. VALERI,[*] M. RORTH,[†] C. G. ZAROULIS,[‡]
M. S. JAKUBOWSKI,[§] S. V. VESCERA[||]

From the Naval Blood Research Laboratory
Chelsea, Massachusetts 02150

Eighteen anesthetized baboons were studied to determine the effects of passive hyperventilation and phlebotomy on oxygen transport. After 1 hour of hyperventilation a significant increase in the red cell affinity for oxygen occurred *in vivo*. This was not associated with any significant changes in cardiac output, oxygen consumption, or in lactic acid production. There was a 40% decrease in cerebral blood flow, a 10 mm Hg decrease in the pulmonary artery Po_2 level, and a 17 mm Hg decrease in the jugular venous Po_2 level. After 1 hour of hyperventilation, the plasma inorganic phosphorus level decreased significantly, the red cell ATP level decreased slightly, and the red cell 2, 3 DPG level increased significantly, indicating that inorganic phosphorus had been removed from the blood during hyperventilation. Passive hyperventilation was maintained, and the baboons were bled 32% of their red cell volume. The blood volume was partially restored with non-buffered isotonic saline. One hour after the phlebotomy and volume restoration (2 hours of hyperventilation) there were no changes in oxygen consumption, cardiac output, cerebral blood flow, or blood lactate levels, but the pulmonary artery Po_2 level was decreased by 15 mm Hg, and the jugular venous Po_2 level was decreased by 20 mm Hg. Systemic oxygen consumption was not affected by the significant decrease in pulmonary artery Po_2.

OXYGEN transport is influenced by ventilation, cardiac output, red cell mass, and red cell affinity for oxygen. It is impaired by an increase in red cell affinity for oxygen *in vivo* and a decrease in red cell mass. The red cell oxygen affinity *in vivo* is influenced by blood pH and Pco_2 levels, and by red cell adenosine triphosphate (ATP) and 2, 3 diphosphoglycerate (2, 3 DPG) levels.[1,2,3,12,13,16,20] We studied the systemic and cerebral oxygen transport in anesthetized baboons that were passively hyperventilated to increase the red cell oxygen affinity *in vivo* and then bled to reduce the oxygen-carrying capacity.

Materials and Methods

Eighteen adult male baboons weighing 19–24 kg were given 1.5 ml of phencyclidine hydrochloride (Sernylan) and 2 ml of pentobarbital (65 mg per ml) intramuscularly for sedation, and that degree of anesthesia was maintained by constant intravenous infusion of pentobarbital throughout the experiment (0.1 mg/kg per minute). Three to 6 mg of curare was given intravenously. Radio-opaque catheters were placed in the femoral artery, the jugular vein, and the pulmonary artery, and their positions were confirmed by x-ray. The catheters were kept open by periodic flushing with an isotonic saline solution containing heparin. The femoral artery catheter was connected to a recorder via a pre-amplifier,[*] and the arterial blood pressure was monitored throughout the experiment. The

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[†] Research Associate, Boston University Medical Center, Boston, Massachusetts and Naval Blood Research Laboratory.

[‡] LCDR, MC, USNR, Research Medical Officer, Naval Blood Research Laboratory.

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This work was supported by the U. S. Navy.

The opinions or assertions contained herein are those of the authors, and are not to be construed as official or reflecting the views of the Navy Department or Naval Service at large.

The animals used in this study were handled in accordance with the provisions of Public Law 89–44 as amended by Public Law 91–579, the "Animal Welfare Act of 1970" and the principles outlined in the "Guide for the Care and Use of Laboratory Animals," U. S. Department of Health, Education and Welfare Publication No. (NIH) 72–23.

[*] Hewlett-Packard, Sanborn Division, Waltham, Mass.

baboons were intubated and connected to a respirator.[*] During the base-line period the respiratory rate was 10–15 per minute with a tidal volume of 10–15 ml/kg. Hyperventilation was induced by increasing the minute ventilation 2 to 2.5 times. The body temperature was monitored by means of an esophageal thermistor probe and was mai tained at 37 C by external heat. After 1 hour of hyperve tilation the animal was bled 1 unit of whole blood (450 m from the arterial catheter within 15 minutes. The volu drawn was immediately replaced by 500 ml of isoton nonbuffered saline solution, and an additional 200–400

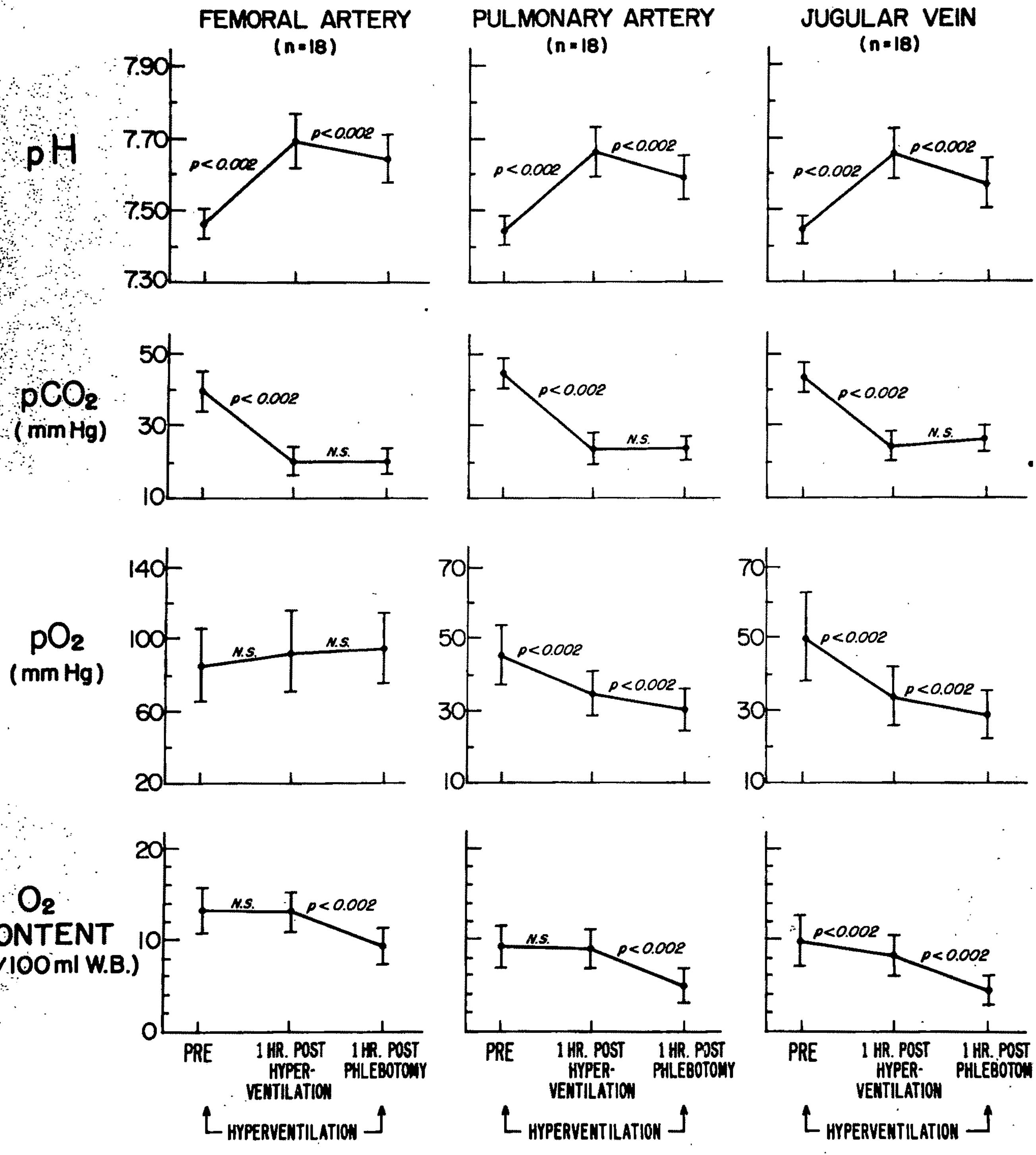

FIG. 1. pH, P_{CO_2}, P_{O_2}, and oxygen content measurements in anaerobic samples from the femoral artery, pulmonary artery, and jugular vein. A measurements are given as mean values for 18 baboons. The p values were derived from the paired t-test, and N.S. indicates a nonsignificant chang

volume of this solution was infused during the postphlebotomy period in order to maintain the blood pressure at near-normal levels. Using a recording spirometer in a closed respiratory circuit, the oxygen consumption was measured before and after 1 hour of hyperventilation, and 1 hour after bleeding (2 hours of hyperventilation). At the time that oxygen consumption was measured, the animal had been breathing about 50% oxygen for 15 minutes, the carbon dioxide was absorbed, and the oxygen consumption was estimated from the reduction in volume of oxygen. The Van Slyke technique was used to measure oxygen consumption independently by the difference in oxygen content between inspired and expired air.

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[*] Model 607, Harvard Apparatus Co., Dover, Mass.

From each of the three catheters, anaerobic blood samples were drawn in heparinized, gas-tight glass syringes before and after 1 hour of hyperventilation, and 1 hour after phlebotomy (2 hours of hyperventilation). The samples were kept on ice, and measurements were performed within 45 minutes of collection. The pH, Po_2, and Pco_2 values were measured by means of the appropriate electrodes calibrated with gases of known composition.[*] Oxygen content was measured in a fuel-cell[†] which was calibrated with dry air.[23] A 50 ul aliquot from the venous sample was equilibrated for 10 minutes in an Astrup microtonometer with a humidified gas mixture containing 30% oxygen, 5% carbon dioxide, and 65% nitrogen, and the oxygen content was measured. This value represents the oxygen-carrying capacity. The oxygen saturation was calculated from the actual oxygen content and the oxygen-carrying capacity with correction for the oxygen dissolved in the blood. From the measured Po_2 and the calculated oxygen saturation, the P_{50} value was calculated using the Hill equation: O_2 Sat. = $K(Po_2n/1 + Po_2n)$ and assuming an n value of 2.7 (in accordance with *in vitro* findings of the oxyhemoglobin dissociation curve of baboon blood). The P_{50} values for samples from the jugular venous and the pulmonary artery blood did not differ significantly. The average variation between the two P_{50} values was less than 1.3 mm Hg, so the two were combined and reported as the average value. Samples with oxygen saturation values of less than 25% and greater than 75% were not used in the study.

Heparinized blood was collected for measurement of red cell 2,3 DPG, ATP, and inorganic phosphorus levels as previously described.[22] Blood lactate (umoles per ml whole blood) was measured spectrophotometrically.[10] The red cell volume was measured using a ^{51}Cr technique.[22] The hemoglobin mass was calculated from the red cell volume and mean corpuscular hemoglobin concentration (MCHC). Approximately 75-100 ml of whole blood was drawn at each sampling.

The cardiac output was calculated from the measured oxygen consumption and the difference in oxygen content between the blood obtained from the femoral artery and pulmonary artery. Cerebral blood flow was calculated from the assumed constant cerebral oxygen consumption and the measured difference in oxygen content between the femoral artery and jugular vein.

Results

Effects of Hyperventilation

Figure 1 shows the pH, Po_2, Pco_2, and oxygen content measurements in blood from the jugular vein, pulmonary artery, and femoral artery. Hyperventilation induced an alkalosis with an increase in arterial pH of about 0.21 pH units and a fall in Pco_2 to 20 mm Hg. The P_{50} value of the venous blood was decreased by 7 mm Hg (Fig. 2). There was no significant change in systemic oxygen extraction (Fig. 3) or in oxygen consumption (Fig. 3). When the oxygen consumption and oxygen extraction were constant, and the red cell oxygen affinity was increased *in vivo*, the samples from the pulmonary artery showed a decrease of about 10 mm Hg in the mixed venous Po_2 (Fig. 1). The significant increase in oxygen extraction by the brain (i.e., the difference between oxygen content of femoral artery

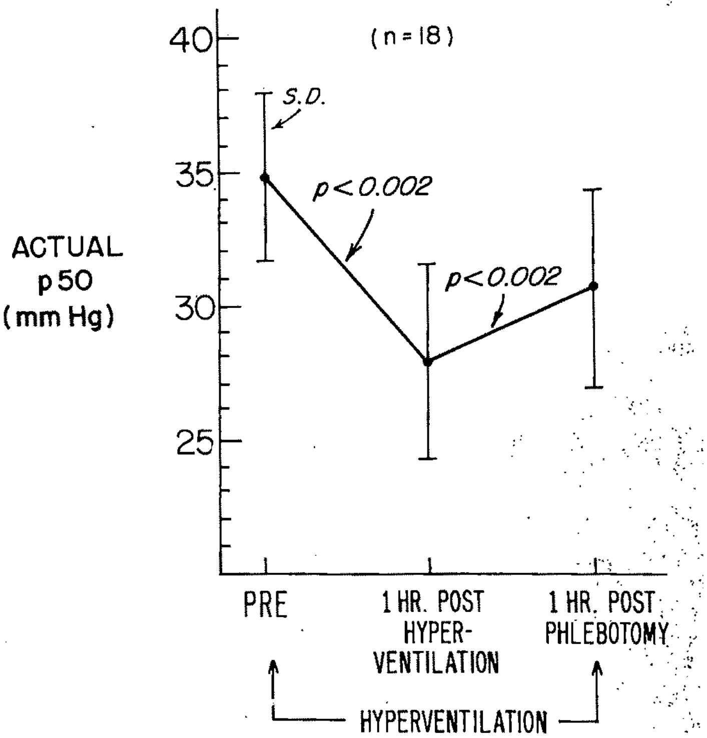

FIG. 2. Changes in red cell oxygen affinity after 1 hour of hyperventilation, and 1 hour after phlebotomy and partial restoration of the blood volume (2 hours of hyperventilation). The P_{50} value was calculated from the measured Po_2 and the measured oxygen saturation. The P_{50} value represents the Po_2 at which 50% saturation of the hemoglobin occurred at the *in vivo* conditions. Measurements in the samples from the jugular vein and pulmonary artery are reported as mean values.

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[*] Instrumentation Laboratory, Lexington, Mass.

[†] Lex O_2 CON, Lexington Instruments, Waltham, Mass.

blood and jugular venous blood) during hyperventilation (Fig. 3) was associated with a 17 mm Hg decrease in the jugular venous Po_2 (Fig. 1) and a 40% decrease in cerebral blood flow. The arterial blood pressure decreased slightly during hyperventilation, but there was no change in the heart rate (Fig. 4).

There was a significant correlation between pH and P_{50} both before and after hyperventilation (Fig. 5). In all studies a Bohr correction factor ($\Delta \log P_{50}/\Delta/\text{pH}$) of -0.49 ± 0.05 (standard deviation (S.D.)) was calculated from the P_{50} measurements before (mean 34.7 mm Hg ± 3.1 S.D.) and after hyperventilation (mean 27.7 mm Hg ± 3.7 S.D.).

Some of the baboons were anemic at the beginning of the experiment, and there was a significant negative correlation between the degree of anemia and the red cell 2, 3 DPG level (Fig. 6), but no such correlation between the P_{50} value and the arterial oxygen content. The red cell ATP and 2,3 DPG and blood inorganic phosphorus values that are reported for each sampling period are the mean values for samples from the pulmonary artery, femoral artery, and jugular vein. There was a 50% decrease in the blood inorganic phosphorus level after 1 hour of hyperventilation, a slight insignificant decrease in the red cell ATP level, and a small but significant increase in red cell 2, 3 DPG (Fig. 7 and Table 2). There were no significant changes in the blood lactate levels in samples from the femoral artery, pulmonary artery, or jugular vein after 1 hour of hyperventilation.

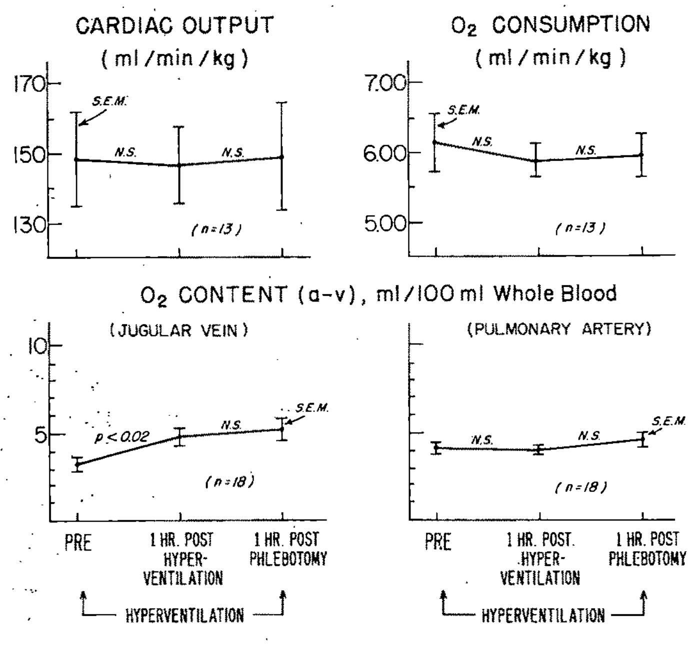

FIG. 3. Cardiac output and oxygen consumption after 1 hour of hyperventilation, and 1 hour after phlebotomy and blood volume restoration (2 hours of hyperventilation). The differences in oxygen content between the femoral artery and pulmonary artery and between the femoral artery and jugular vein are shown.

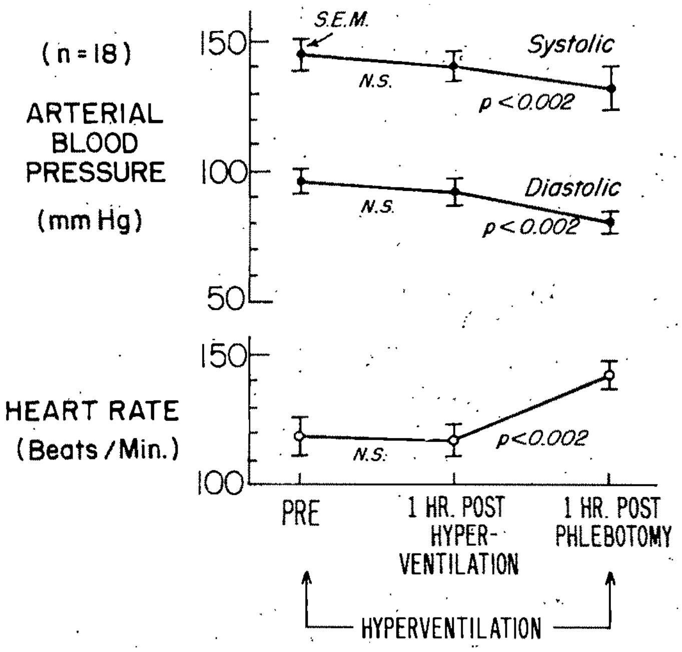

FIG. 4. Femoral artery blood pressure and heart rate before and after 1 hour of hyperventilation, and 1 hour after phlebotomy and blood volume restoration (2 hours of hyperventilation).

Effects of Phlebotomy

One hour after phlebotomy (2 hours of hyperventilation) the blood pH decreased significantly whereas the Pco_2 was constant (Fig. 1). There was no significant change in the systemic or cerebral oxygen extraction (Fig. 3). There was a significant increase in the P_{50} value 1 hour after phlebotomy (2 hours of hyperventilation) (Fig. 2). The amount of hemoglobin bled constituted about 32% of the total hemoglobin mass (Table 1), and the oxygen content of the arterial blood was reduced by about 28% (Fig. 1). The oxygen consumption remained constant (Fig. 3). Replacement of the shed blood with 1½ to 2 times the volume of isotonic nonbuffered saline solution produced a 10 mm Hg fall in blood pressure and a 20% increase in heart rate (Fig. 4). One hour after phlebotomy the pulmonary artery and jugular venous Po_2 values decreased significantly (Fig. 1). There were no significant changes in the lactate levels in the blood from the femoral artery, pulmonary artery, or jugular vein.

Discussion

As in man, the red cell affinity for oxygen in the baboon is regulated by hydrogen ion, carbon dioxide, and red cell 2, 3 DPG and ATP. The actual P_{50} value represents the red cell affinity for oxygen at the *in vivo* conditions of temperature, blood pH, carbon dioxide, and the red cell 2, 3 DPG, ATP, and inorganic phosphorus levels. The increase in red cell oxygen affinity *in vivo* produced by hyperventilation was associated with decreases in carbon dioxide and hydrogen ion concentrations, a slight insignifi-

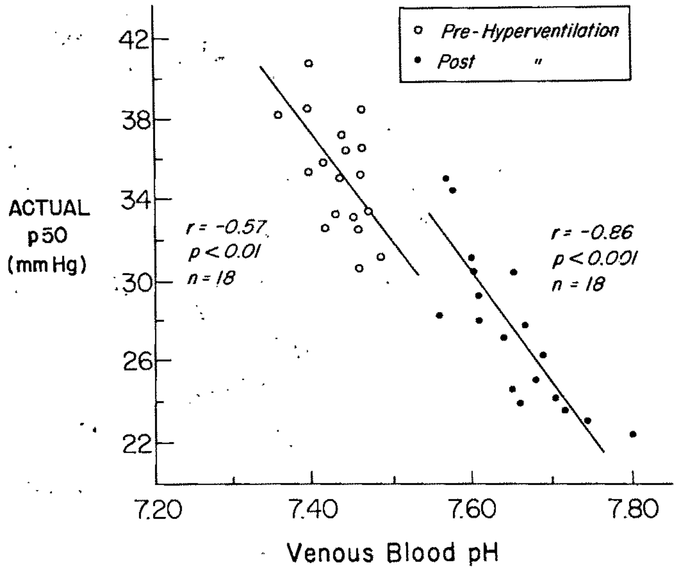

Fig. 5. Relation between actual P_{50} value and venous blood pH prior to and after 1 hour hyperventilation. The measurements in the samples from the jugular vein and pulmonary artery are reported as mean values.

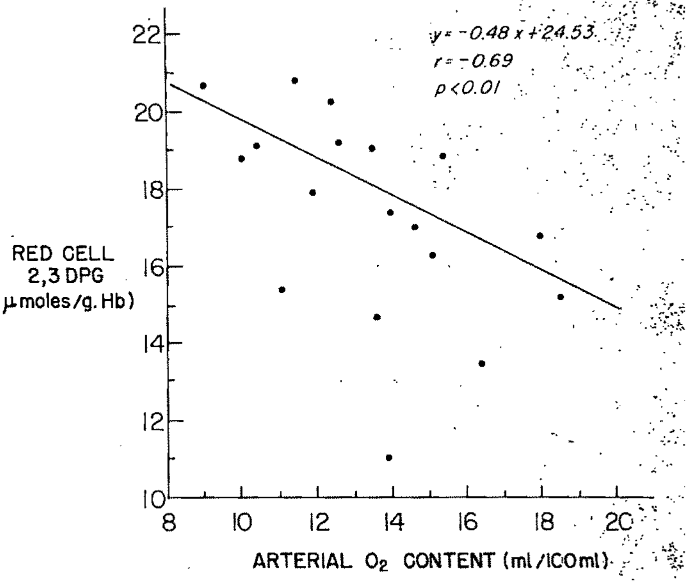

Fig. 6. Relation between red cell 2, 3 DPG and oxygen content in samples from the femoral artery.

cant decrease in the ATP level, and a small but significant increase in the red cell 2, 3 DPG level. The calculated Bohr correction factor of −0.49 was similar to that of −0.52 observed in human blood *in vitro*.[24] There was a decrease in red cell affinity associated with a decrease in blood pH 1 hour after phlebotomy. The decrease in blood pH was not accompanied by an increase in the blood lactate level.

The slight decrease in red cell ATP, and the small increase in red cell 2, 3 DPG during hyperventilation (Fig. 7) probably reflected the combined effects of pH and inorganic phosphorus on red cell metabolism. An increase in red cell pH *in vitro* produces an increase in red cell 2, 3 DPG and a decrease in ATP.[17] Haldane *et al.*[9] reported a rapid and significant reduction in both the plasma concentration and the urinary excretion of inorganic phosphorus after hyperventilation. Similar findings were reported by George *et al.*,[7] who suggested that the inorganic phosphorus was used by red cells to increase their ATP and 2, 3 DPG levels. However, our results reported in Table 2 suggest that during hyperventilation inorganic phosphorus left the blood and was taken up by other tissue.[19]

We found a negative correlation between the baseline

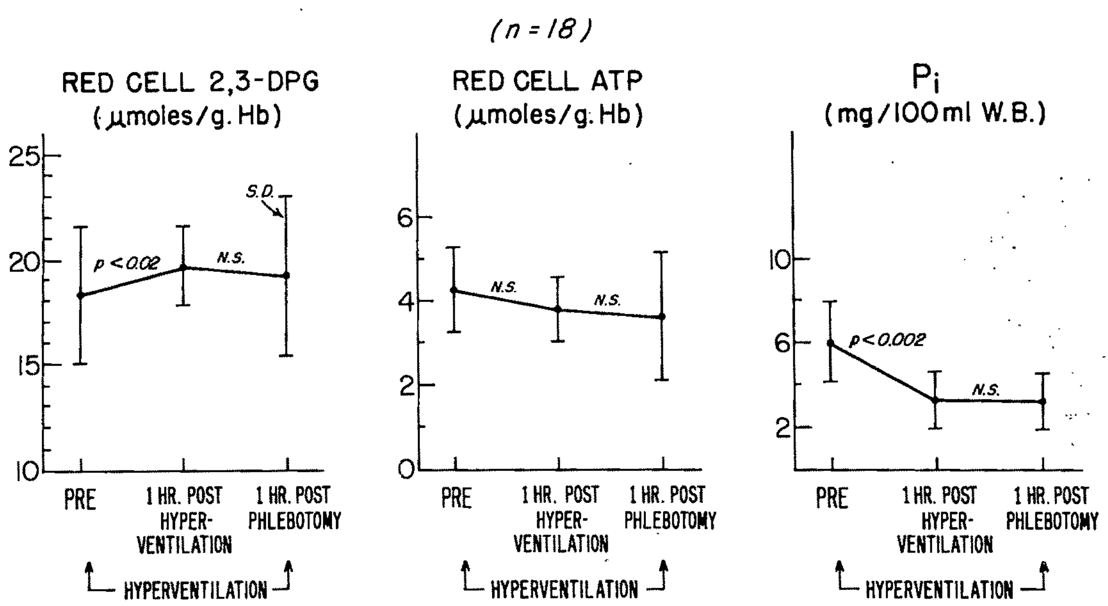

Fig. 7. Red cell ATP and 2,3 DPG levels and whole blood inorganic phosphorus level after 1 hour of hyperventilation, and 1 hour after phlebotomy and blood volume restoration (2 hours of hyperventilation).

TABLE 1. *Blood Volume and Red Cell Mass Prior to Phlebotomy, and Amount of Hemoglobin Bled*

Blood Volume (ml)	Hemoglobin Mass (g)	Hemoglobin Bled (g)	Percent of Original (%)
1110 ± 246	89.7 ± 27.6	41.8 ± 8.6	32.4 ± 5.9

Mean ± S.D., n = 18

red cell 2, 3 DPG level and the arterial oxygen content: this finding parallels that observed in human blood of a negative correlation between the hemoglobin concentration and the red cell 2, 3 DPG level.[6,11] There was no correlation between the 2, 3 DPG level and the red cell affinity for oxygen *in vivo* (Figs. 2 and 7).

The increase in red cell oxygen affinity produced by hyperventilation did not affect the systemic oxygen extraction, oxygen consumption, or cardiac output (Fig. 3).

An increase in red cell oxygen affinity accompanied by a constant oxygen extraction produced a decrease in the mixed venous Po_2 (Fig. 1). Cain[4] who studied the dog, and Riggs *et al.*[18] who studied the rhesus monkey, reported that passive hyperventilation increased oxygen consumption. However, in our study of the baboon we found no significant change in oxygen consumption.

No significant changes were observed in systemic oxygen extraction, oxygen consumption, or cardiac output 1 hour after acute reduction in red cell volume and partial restoration of the blood volume with a crystalloid solution (2 hours of hyperventilation). Other investigators have reported increased cardiac output when the subjects had an anemia of 6 g of hemoglobin or less per 100 ml of blood or when the hematocrit value was 20 V% or less.[14,15]

In our study the pulmonary artery Po_2 level reflected the blood flow and oxygen extraction. Although a decrease in pulmonary Po_2 of about 15 mm Hg occurred 1 hour after phlebotomy (2 hours of hyperventilation), the cardiac output was unchanged. The systemic oxygen consumption remained constant throughout the experiment, and we assumed that the oxygen consumption by the brain did likewise. The significantly increased oxygen extraction by the brain during hyperventilation (Fig. 3) indicated a 40% reduction in cerebral blood flow. A 7 mm Hg increase in red cell affinity for oxygen *in vivo* and a 40% decrease in cerebral blood flow led to a 17 mm Hg decrease in jugular venous Po_2. This was greater than that found in the pulmonary artery which contains mixed venous blood from the entire body (Fig. 1). These findings agree with those of other investigators on the effect of carbon dioxide on cerebral blood flow.[21] One hour after phlebotomy and partial restoration of the blood volume (2 hours of hyperventilation), there was no change in cerebral blood flow.

Guyton[8] has suggested that the Po_2 in the arterioles directly affects the smooth muscle cells in the vessel wall and regulates local blood flow. In our study, the increased red cell affinity for oxygen *in vivo* and decreased oxygen-carrying capacity produced decreases in Po_2 in the blood obtained from the pulmonary artery and the jugular vein, but this decrease had no significant effect on cardiac output or cerebral blood flow. Our findings of decreased Po_2 levels in blood obtained from the pulmonary artery, normal oxygen consumption, and normal blood lactate levels support the observations of Chance and associates[5] that normal mitochondrial activity is maintained at very low Po_2 tensions.

TABLE 2. *Effects of Hyperventilation on Plasma and Red Cell Organic and Inorganic Phosphate Compounds*

Inorganic Phosphate (mmoles/l plasma)	Inorganic Phosphate (mmoles/l RBC)	Red Cell 2, 3 DPG Phosphate (mmoles/l RBC)	Red Cell ATP Phosphate (mmoles/l RBC)	Inorganic Phosphate and Organic Phosphate (mmoles/l RBC)
		Pre		
2.0 ± 0.8	1.9 ± 0.9	11.9 ± 2.2	4.1 ± 0.9	17.9 ± 2.1
		1 Hour Post Hyperventilation		
1.2 ± 0.5	0.9 ± 0.4	12.9 ± 2.0	3.8 ± 0.9	17.6 ± 2.1

Mean ± S.D., n = 18.

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Physiologic Effects of Transfusing Red Blood Cells With High or Low Affinity for Oxygen to Passively Hyperventilated, Anemic Baboons:

Systemic and Cerebral Oxygen Extraction

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Anemic, passively hyperventilated baboons were given preserved red blood cells either with increased or with slightly reduced affinity for oxygen to restore the red cell volume. In the high affinity group there was a 50% increase in cerebral blood flow immediately after the transfusion, but there was no significant change in the low affinity group. The cardiac output decreased slightly in the low affinity group, and increased slightly but insignificantly in the high affinity group. Two hours after transfusion the cerebral blood flow had returned to normal in the high affinity group. In both groups there was a decrease in arterial blood pH and an increase in P_{O_2} in blood from the pulmonary artery and the jugular vein after transfusion. A 40% restoration of the 2,3 DPG level occurred within 4 hours of the transfusion of red cells with high affinity for oxygen, and this rapid increase was associated with increases in blood pH and inorganic phosphorus levels. Preserved red cells with high affinity for oxygen and low 2, 3 DPG levels significantly increased the cerebral circulation during the 2-hour posttransfusion period. These findings lend support to the recommendation that preserved red cells with normal or elevated 2,3 DPG levels be administered to patients in hemorrhagic or septic shock, and to patients subjected to extracorporeal circulation during cardiac surgery in order to lessen the demand for increased blood flow and to ensure adequate tissue oxygenation during the postoperative period.

THE PURPOSE of red blood cell transfusion is to increase the oxygen-carrying capacity and oxygen delivery to tissue. The oxygen-carrying capacity is increased when the red cell volume is increased after transfusion. The oxygen delivery to tissue, on the other hand, is influenced by the affinity for oxygen of the preserved red cells. Valtis and Kennedy[20] in 1954 described the dissociation between the oxygen-carrying and releasing properties of preserved red cells. Red cells stored at 4 C in ACD for 7 days maintain their ability to circulate and carry oxygen, but their ability to release it is impaired. In 1967, Benesch and Benesch[1] and Chanutin and Curnish[2] reported the importance of red cell 2,3 DPG in the oxygen transport function.

When red blood cells are stored for more than 2 weeks in the liquid anticoagulants, acid-citrate-dextrose (ACD) and citrate-phosphate-dextrose (CPD), they become depleted of 2,3 diphosphoglycerate (2,3 DPG) and have increased red cell affinity for oxygen,[4,18] resulting in impaired oxygen transport function. In a study of 20- to 40-year-old stable, anemic patients with traumatic injuries, the transfusion of preserved red cells with increased affinity for oxygen produced an increase in cardiac output during the 4-hour posttransfusion period.[16] Since patients with anemic hypoxia-

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The animals used in this study were handled in accordance with the provisions of Public Law 89-44 as amended by Public Law 91-579, the 'Animal Welfare Act of 1970' and the principles outlined in the 'Guide for the Care and Use of Laboratory Animals,' U. S. Department of Health, Education and Welfare Publications No. (NIH) 72-23.

TABLE 1. *Composition of Rejuvenation Solution*[*]

Pyruvic Acid	11 g/l = 100 mmoles/l
Inosine	26.8 g/l = 100 mmoles/l
Na_2HPO_4	28.4 g/l = 200 mmoles/l
Adenine	0.675 g/l = 5 mmoles/l
Glucose	18.0 g/l = 100 mmoles/l
NaCl	9.0 l = 150 mmoles/l

pH 7.2 – 7.3.

[*] 50 ml of this mixture was added to a unit of blood.

who require therapeutic transfusion usually have 2,3 DPG levels elevated to 1½ to 2 times normal,[18] they should receive preserved red cells with 2,3 DPG levels most similar to their own. The 2,3 DPG and adenosine triphosphate (ATP) levels of preserved red cells can be restored to normal or even elevated by incubating the red cells in a pyruvate, inosine, glucose, phosphate, adenine (PIGPA) solution.[5,11,15,17,18]

We studied baboons to determine the physiologic effects of the transfusion of red cells with low 2,3 DPG levels and increased affinity for oxygen, and red cells with slightly elevated 2,3 DPG levels and decreased affinity for oxygen. Baboons were used because their red cells are similar to those of man with regard to regulation of red cell metabolism and oxygen affinity,[8] and primates have an internal jugular vein that receives blood exclusively from the brain.[10] The anesthetized baboons were passively hyperventilated to produce hypocapnia and alkalosis which, in turn, produce a decrease in cerebral blood flow and an increase in red cell affinity for oxygen. They were then acutely bled one-third of their red cell volume. The blood volume was partially restored with sodium chloride solution, and hyperventilation was maintained throughout the study. We studied preserved red cells with increased affinity for oxygen and with slightly reduced affinity for oxygen to determine their ability to correct an anemic state in passively hyperventilated, normotensive baboons. The observations reported are for the first 4 hours after transfusion.

Materials and Methods

Recipients

Five baboons were transfused with red cells having slightly reduced affinity for oxygen and slightly elevated 2,3 DPG levels, and 6 were transfused with red cells having increased affinity for oxygen and low 2,3 DPG levels. These 11 baboons were part of a group of 18 reported in a companion paper in which the details of passive hyperventilation and phlebotomy of the anesthetized baboons are described.[19]

The paralyzed, passively hyperventilated baboons were phlebotomized 450 ml of whole blood 1 hour prior to transfusion. The volume of the phlebotomy was replaced first with 500 ml of a nonbuffered isotonic saline solution and then with a 200–400 ml volume of the same solution, but this did not restore the blood volume completely. Approximately 300–350 ml of washed, concentrated preserved

TABLE 2. *Data on Transfused Baboon Red Cells*

	Volume (ml)	Red Cell Hemoglobin (g)	Hematocrit (V%)	Bellingham P_{50} (mm Hg)		2, 3 DPG (umoles/g Hb)		ATP (umoles/g Hb)		RBC pH 37 C		Plasma pH 37 C		Blood pH 22 C
				Pre	Washed	Pre	Washed	Pre	Washed	Pre	Washed	Pre	Washed	Washed
Storage at 4 C (Days): 14 ± 1, n = 6						Non-Rejuvenated								
Mean	347	83.4	76.1	23.9	24.0	2.8	2.7	3.0	3.1	6.58	6.90	6.76	7.12	6.97
S.D.	65	26.9	3.6	1.3	2.8	2.0	2.2	0.7	0.9	0.09	0.18	0.09	0.33	0.18
S.E.				0.7	1.1	0.8	0.8	0.3	0.3	0.05	0.07	0.05	0.14	0.08
n				4	6	6	6	6	6	4	6	4	6	5
Storage at 4 C (Days): 12 ± 3, n = 5						Rejuvenated With PIGPA								
Mean	302	78.9	78.4	25.9	41.4	4.6	18.2	3.8	7.0	6.55	6.68	6.81	6.94	6.99
S.D.	63	20.7	4.9	2.4	4.6	2.7	3.7	2.6	1.0	0.16	0.25	0.22	0.28	0.19
S.E.				1.2	2.1	1.2	1.5	1.1	0.4	0.07	0.11	0.10	0.13	0.11
n				4	5	5	5	5	5	5	5	5	5	3
						Fresh Heparinated Baboon Blood								
Mean		11.8	40.0	36.1		17.2		4.8		7.31				
S.D.		1.5	5.7	4.3		2.3		0.7		0.23				
S.E.		0.3	1.0	1.6		0.4		0.1		0.08				
n		27	27	7		28		24		9				

red cells (hematocrit value of about 75%) were given intravenously under 100 mm Hg of pressure. The transfusion was completed within 15 minutes. Blood samples were drawn from the femoral and pulmonary arteries and from the jugular vein. Samples were drawn immediately after transfusion, and 2 and 4 hours later. A total of 75–100 ml of whole blood was drawn during each sampling period. Anaerobically collected blood samples were obtained to measure the pH, Po_2, Pco_2, oxygen content, and oxygen-carrying capacity.[19] The oxygen saturation of hemoglobin and the *in vivo* P_{50} value of the mixed venous blood were measured.[19] Blood was collected in heparin for red cell 2,3 DPG, ATP, lactate, and inorganic phosphorous measurements.[18] The red cell ATP and 2,3 DPG concentrations reported are mean values from the three sampling sites. The red blood cell volume was measured by the ^{51}Cr technique.[13] Oxygen consumption was measured, and cardiac output and cerebral blood flow were calculated as described in the companion paper.[19]

Transfused Blood

Blood was collected in CPD and stored at 4 C for about 14 days. To produce slightly elevated 2,3 DPG levels and slightly reduced affinity for oxygen, the stored red cells were incubated for 1 hour at 37 C with a solution containing pyruvate, inosine, glucose, phosphate, and adenine (PIGPA) in the concentrations listed in Table 1. A 50 ml volume of the solution was added to each unit. After incubation, the blood was washed with 2 L of isotonic sodium chloride solution containing 200 mg% glucose and 200 mg% disodium phosphate, with a pH of about 7.6. Previous investigations have shown that the washing procedure effectively removes the inosine and adenine.[15,17] The stored red blood cells with low 2,3 DPG levels and increased affinity for oxygen were incubated at 37 C for 1 hour without any rejuvenation solution and washed as described above. Both the rejuvenated and the nonrejuvenated washed red cells had hematocrit values of about 75%.

The 24-hour survival values were not significantly different in the liquid-stored washed red cells whether they were rejuvenated or not (Valeri, to be published). The transfused red cells were type specific.

Results

Pertinent measurements are reported in Table 2.

Fig. 1 shows the measured values of pH, Po_2, Pco_2, oxygen content, and arterio-venous oxygen content difference. The effects of hyperventilation and phlebotomy are reported in

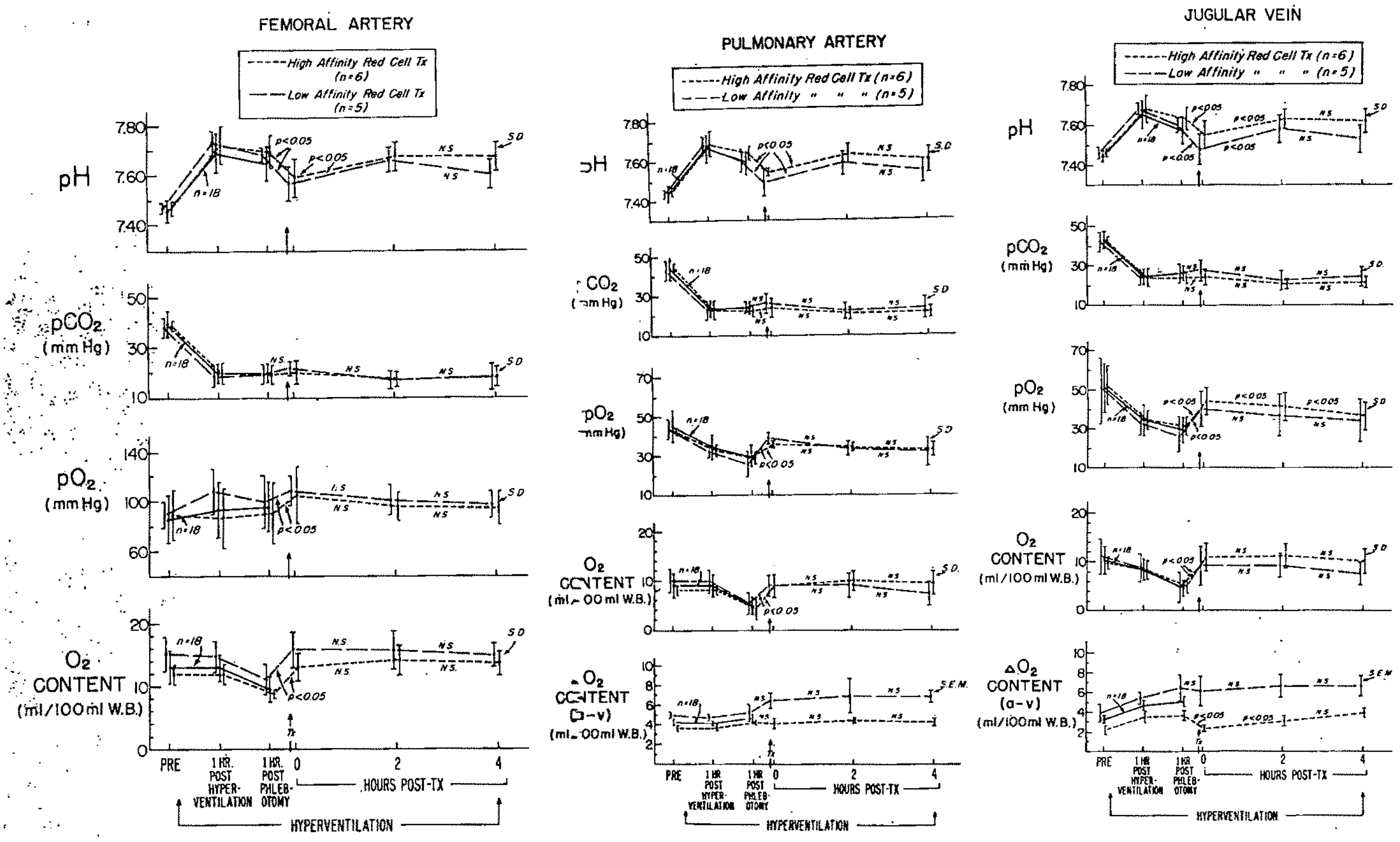

FIG. 1. pH, Po_2, Pco_2, and O_2 content measurements in anaerobically collected blood from the femoral artery, pulmonary artery, and jugular vein before and after transfusion. In the latter two the arterio-venous differences in O_2 content are included. The effects of hyperventilation and phlebotomy in 18 baboons are reported, as well as data on transfusions of red cells with low oxygen affinity to 5 baboons and transfusions of red cells with high oxygen affinity to 6 baboons.

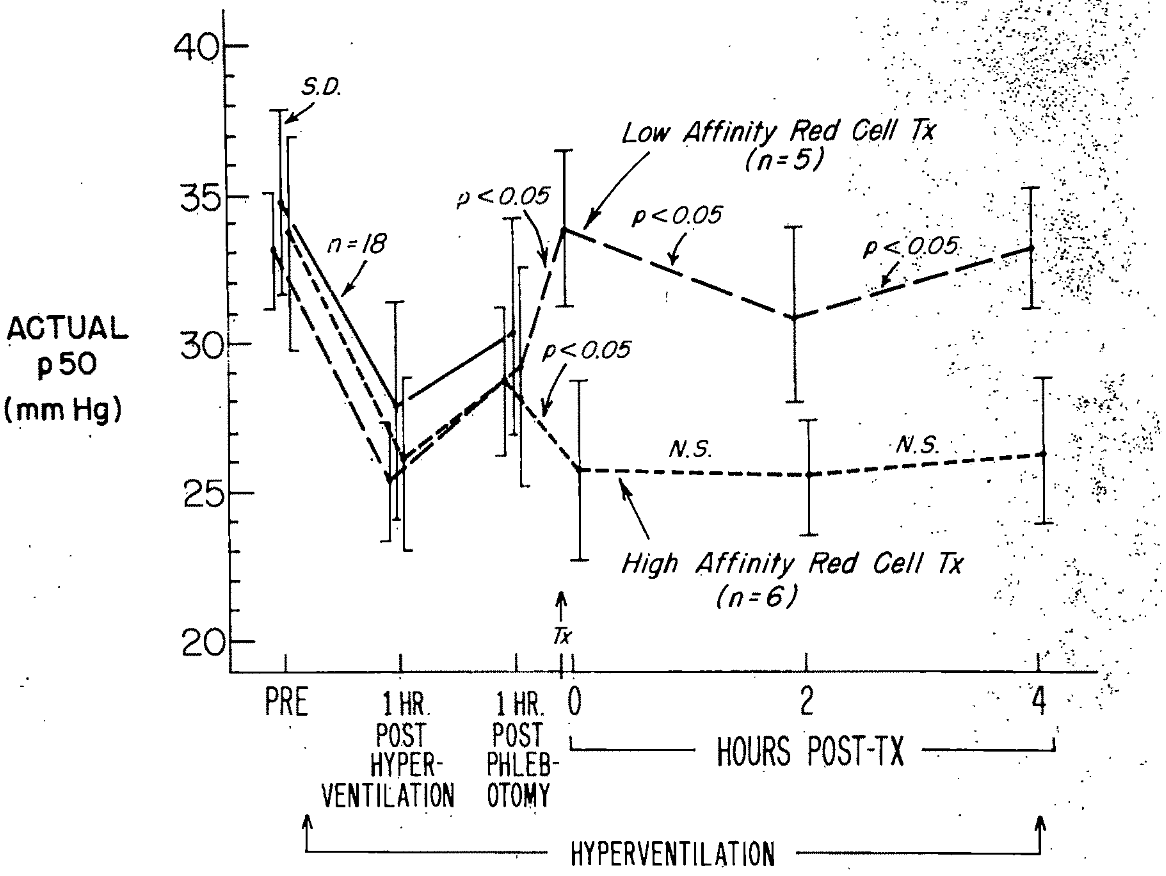

FIG. 2. Actual P_{50} values in mixed venous blood prior to and for 4 hours after transfusion. The actual P_{50} value is the Po_2 in mm Hg which produced 50% oxygen saturation of the hemoglobin at the condition *in vivo*.

the companion paper and also are included in the figures.[19] Six baboons received red cells with increased affinity for oxygen, and 5 baboons received red cells with slightly reduced affinity for oxygen. Decreases in blood pH and increases in mixed venous and jugular venous Po_2 occurred when the blood Pco_2 was constant, whether the transfused red blood cells had increased or decreased affinity for oxygen. The difference in oxygen content between the femoral artery and the jugular vein decreased significantly ($p < 0.05$, paired t-test)[7] following transfusion of red blood cells with increased affinity for oxygen, but no significant change was observed when transfused red blood cells had slightly reduced affinity for oxygen (Fig. 1). The difference in oxygen content between the femoral artery and the pulmonary artery increased in all 5 baboons following the transfusion of low affinity red blood cells, but there was no change in any of the 6 baboons that received high affinity red cells (Fig. 1).

Figure 2 shows the changes in red cell oxygen affinity *in vivo* before and for 4 hours after the transfusion. The Po_2

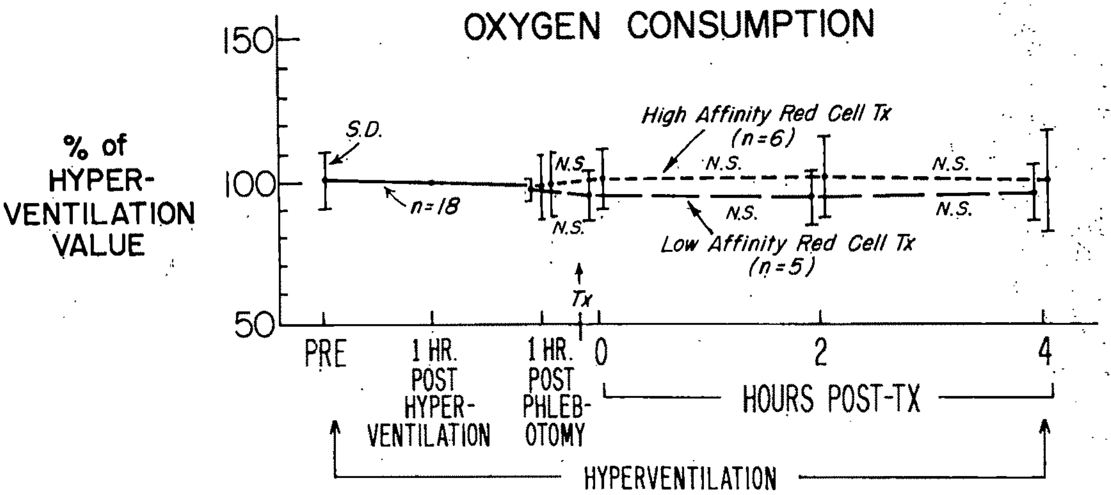

Fig. 3. Oxygen consumption prior to and for 4 hours after transfusion. The values are calculated as a percentage of the value obtained after 1 hour of hyperventilation.

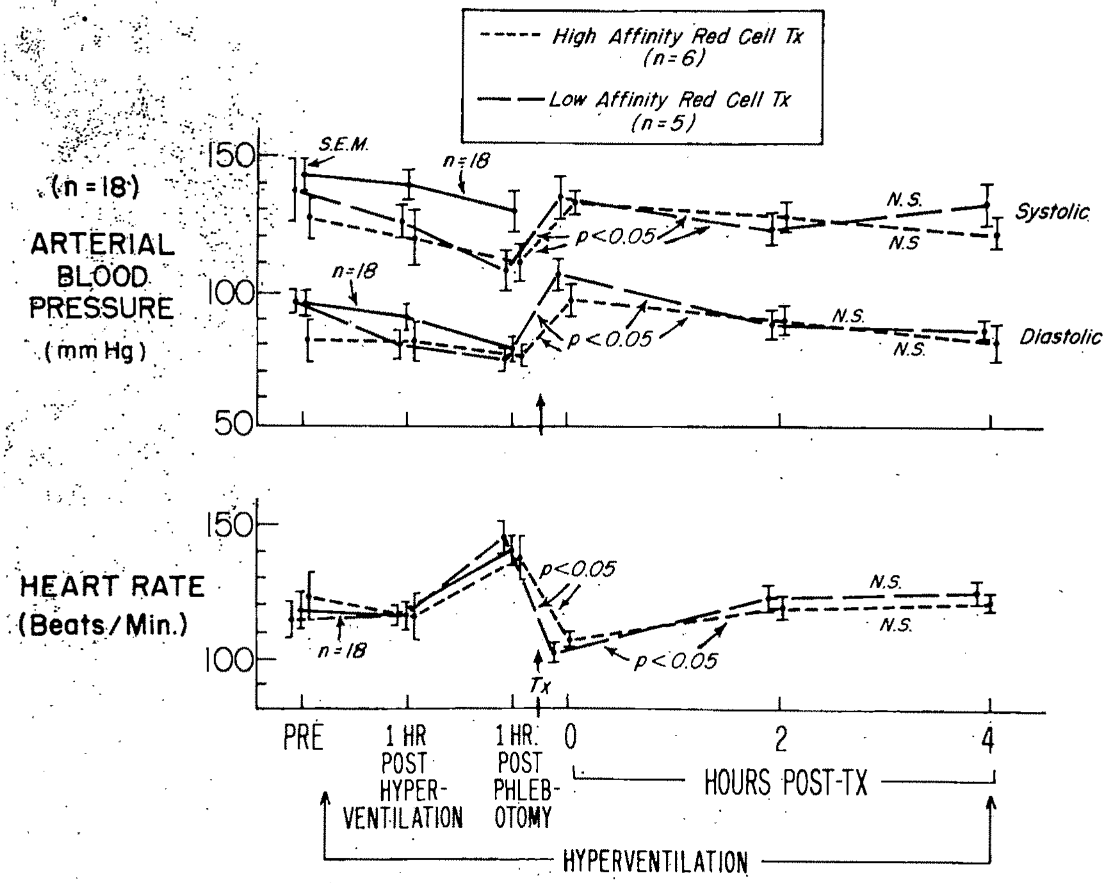

Fig. 4. Femoral arterial blood pressure and heart rate prior to and for 4 hours after transfusion.

(mm Hg) at which 50% of the hemoglobin is oxygenated at the *in vivo* condition of pH and Pco_2 is the actual P_{50} value. There was no significant change in oxygen consumption throughout the study (Fig. 3). Significant increases in the systolic and the diastolic arterial blood pressure were found immediately after the transfusion, but this returned to normal within 2 hours after the transfusion (Fig. 4). Conversely, the heart rate decreased immediately after transfusion, and returned to normal within 2 hours (Fig. 4). This was true in both groups to a similar degree.

The absence of change in systemic oxygen consumption convinced us that cerebral oxygen consumption was constant throughout the study. When oxygen consumption is constant, the blood flow can be calculated from the arterio-venous difference in oxygen content (Fick principle). Using this approach, the cerebral blood flow and cardiac output were estimated, and the relative changes are reported in Fig. 5. The value after 1 hour of hyperventilation was used as the 100% value. A 50% increase in cerebral blood flow and a slight but insignificant increase in cardiac output occurred immediately following transfusion of red cells with low 2,3 DPG and with increased affinity for oxygen. Within 2 hours after transfusion of high affinity red cells, the cerebral blood flow returned to the pre-transfusion level. There was no significant change in cerebral blood flow or cardiac output following transfusion of red cells with slightly increased 2,3 DPG and with decreased affinity for oxygen. Figure 6 shows the changes in the red blood cell 2,3 DPG and ATP, and the blood inorganic phosphorus levels. The lactate levels did not change in either the red blood cells with increased affinity for oxygen or those with slightly decreased affinity (Fig. 7).

Discussion

In this study the Pco_2 level was maintained at 20 mm Hg and the pH of arterial blood was never below 7.56 in either experimental group of baboons.

The actual P_{50} value was influenced by the red cell 2,3 DPG and ATP levels, and blood pH and Pco_2. It was increased when there was a decrease in pH or increases in ATP and 2,3 DPG, and it was decreased when there was an increase in pH or a decrease in ATP and 2,3 DPG.

The transfusion of red blood cells with low 2,3 DPG levels produced a decrease of about 3.0 mm Hg in the actual P_{50} value immediately after transfusion. This decrease reflected the low 2,3 DPG level and the decrease in blood pH. Immediately after the transfusion of red blood cells having slightly elevated 2,3 DPG levels, there was an increase of about 5.0 mm Hg in the actual P_{50} value, reflecting the slightly increased 2,3 DPG level and the decrease in blood pH.

Within 4 hours after transfusion of red cells low in 2,3

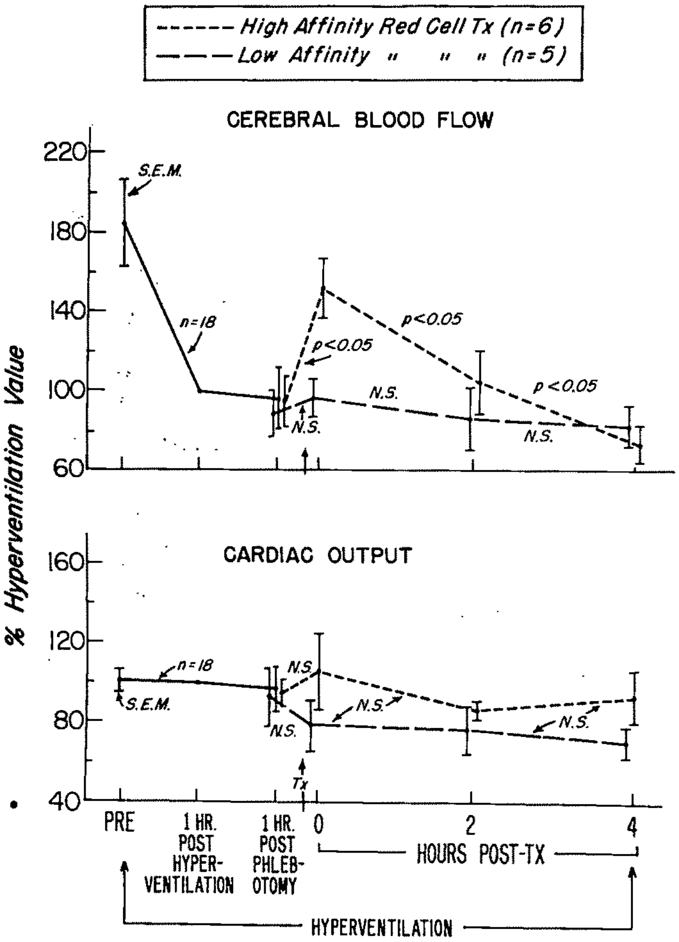

Fig. 5. Cardiac output as calculated from the measured oxygen consumption and the difference in oxygen content between the femoral artery and the pulmonary artery. The cerebral blood flow was calculated from an assumed constant oxygen consumption by the brain and the difference in oxygen content between the femoral artery and the jugular vein. The cerebral blood flow and the cardiac output are reported as a percentage of the value obtained after 1 hour of hyperventilation.

DPG, the level was restored to about 40% of normal (Fig. 6). This rate of restoration in the baboon is more rapid than has been reported in man following the transfusion of stored red blood cells low in 2,3 DPG.[14] The alkaline pH and the high concentrations of blood inorganic phosphorus produce decreases in 2,3 phosphatase activity which, in turn, may increase the 2,3 DPG level.[5] The baboons that received red blood cells with low 2,3 DPG levels had significantly lower blood inorganic phosphorus concentrations during the 2-hour posttransfusion period than did the baboons that received red blood cells with slightly increased 2,3 DPG levels; this reflected the utilization of inorganic phosphorus associated with increased 2,3 DPG (Fig. 6).

The increase in the red cell 2,3 DPG level which persisted for 4 hours after the transfusion of red cells with slightly elevated 2,3 DPG levels was greater than could be attributed to the donor's level and the recipient's pretransfusion level. One possible explanation is that the transfused red cells contained an excess of precursor compounds for 2,3 DPG synthesis which were converted to 2,3 DPG following transfusion.

The red cells that had slightly increased 2,3 DPG levels also had elevated ATP levels, and the ATP level increased immediately following transfusion (Fig. 6). The subsequent decrease in the ATP level during the 4-hour posttransfusion period was associated with a slight increase in blood pH.

Since oxygen consumption was constant throughout the experiment (Fig. 3), we assumed that the brain oxygen consumption was also constant. Changes in arterio-venous difference in oxygen content in the systemic and cerebral circulation reflected changes in cardiac output and cerebral blood flow. Immediately after transfusion of preserved red cells with increased affinity for oxygen and low 2,3 DPG level there was a significant increase of about 50% in cerebral blood flow without any change in blood lactate levels (Figs. 5 and 7). What role the red cell 2,3 DPG level may have played in the cerebral blood flow increase is not clear. After transfusion of preserved red cells with low affinity for oxygen and slightly increased 2,3 DPG level

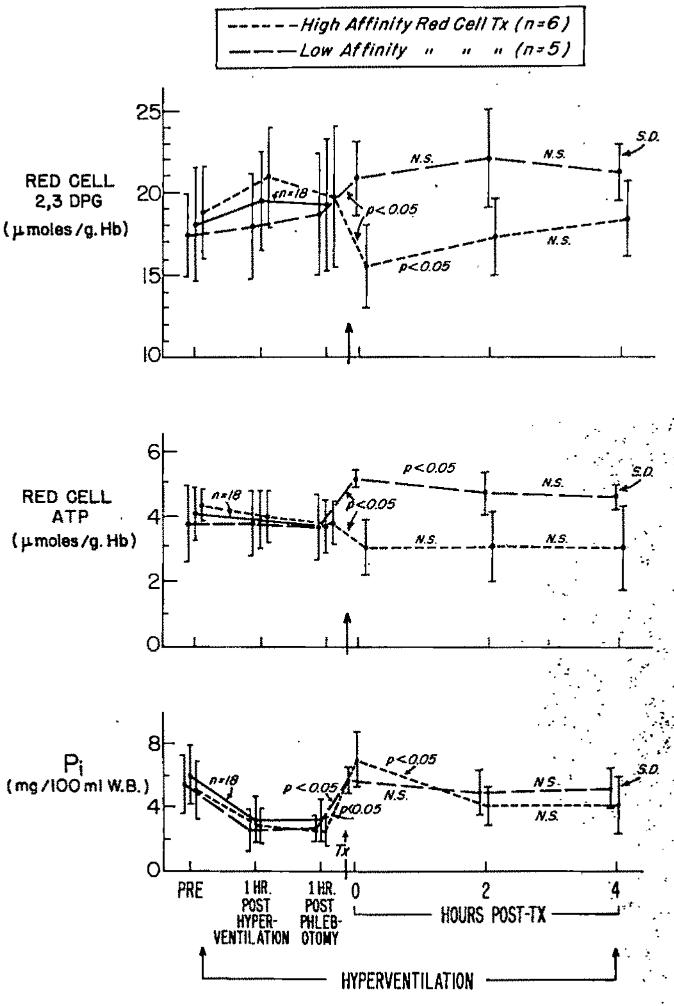

Fig. 6. Red cell 2, 3 DPG and ATP levels, and blood inorganic phosphorus levels prior to and for 4 hours after transfusion.

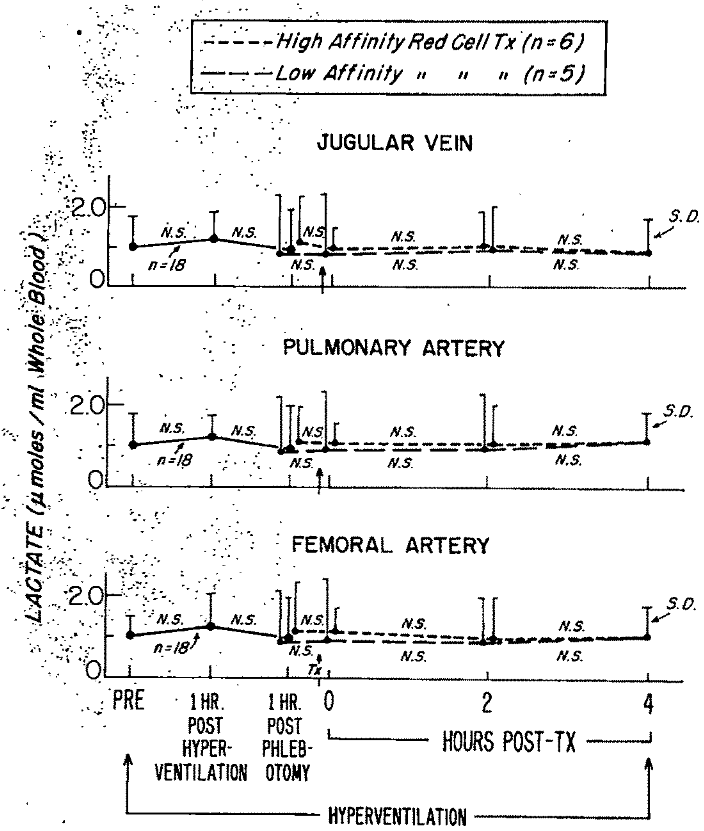

FIG. 7. Blood lactate levels in the femoral artery, pulmonary artery, and jugular vein prior to and 1 hour after hyperventilation, after 1 hour of phlebotomy (2 hours of hyperventilation), and for 4 hours after the transfusions of red cells with increased or decreased affinity for oxygen.

there was no change in the Pco_2, and the cerebral blood flow did not change. The differences in cerebral blood flow between the two groups immediately after transfusion disappeared within 2 hours, but the differences in red cell affinity for oxygen did not (Figs. 2 and 5). There was an insignificant increase in cardiac output after the transfusion of red cells with increased affinity for oxygen, but only a slight decrease after transfusion of red cells with decreased affinity for oxygen (Fig. 5).

The increase in blood volume following the transfusion of high affinity and low affinity red cells produced significant increases in systolic and diastolic arterial blood pressure, and a decrease in the heart rate. An increase in blood pressure at constant or decreased cardiac output indicated an increase in peripheral vascular resistance. The peripheral vascular resistance decreased during the first 2 hours after transfusion, during which time the blood pressure returned to normal and the cardiac output was constant. The systemic blood flow changes were much less pronounced than the cerebral blood flow changes.

Circulating red cells with increased affinity for oxygen *in vivo* may pose a demand for increased blood flow. They may also decrease the mixed venous Po_2 and tissue Po_2. Riggs, Shafer, and Guenter[12] have reported on the effects of exchange transfusions of autologous red blood cells with low 2,3 DPG levels and increased affinity for oxygen in rhesus monkeys. They found a significant decrease in the mixed venous Po_2 tension without evidence of acidosis, decreased oxygen consumption, or a compensatory increase in cardiac output. The mixed venous oxygen tension is influenced by cardiac output, red cell mass, and red cell affinity for oxygen. The differences between the mixed venous Po_2 levels in our study and those found by Riggs *et al.*[12] might be explained in part by the differences in red cell mass after the transfusion in the two studies.

Holsinger, Salhany, and Eliot[9] studied the physiologic effect of red cells with low 2,3 DPG and increased affinity for oxygen on the canine myocardium. Anterior myocardial infarction was produced in 4 dogs, and after 2 months of recuperation, the circumflex coronary artery was partially constricted to produce left ventricular failure. The left coronary artery was then perfused at a constant flow rate with preserved red cells depleted of 2,3 DPG and with increased affinity for oxygen, producing further cardiac decompensation. These investigators suggest that preserved red cells with increased affinity for oxygen produced myocardial ischemia when a constant coronary blood flow was maintained.

Woodson, Wranne, and Detter[21] studied the effect of increased red cell affinity for oxygen on work performance of trained rats. The rats were exchange-transfused with fresh heparinated blood, fresh ACD blood, and liquid-stored red cells with low 2,3 DPG levels. After exchange transfusion with fresh blood, the central venous oxygen pressure remained unchanged at 37 mm Hg. After exchange transfusion with red cells with low 2,3 DPG levels, there was a decrease in central venous oxygen tension of about 12 mm Hg without any apparent adverse effect, and the working ability of the animals was decreased by about 10%. A decrease in hemoglobin concentration of 10% produced a similar reduction in work performance.

Since the brain is sensitive to a lack of oxygen,[3] the well-being of some patients may be placed in jeopardy following transfusion of preserved red cells with increased affinity for oxygen. When patients are not able to meet the demand for increased blood flow, the venous oxygen tension may decrease to critical levels. Human red cells can be prepared so that they have 1½ to 2 times normal 2,3 DPG levels and decreased affinity for oxygen; they have excellent posttransfusion survival and increased oxygen releasing capacity for at least 72 hours after transfusion.[17,18] Red cells prepared in this manner are indicated for patients subjected to extracorporeal circulation during cardiac surgery and for anemic patients with myocardial or cerebrovascular insufficiency. Preserved red cells should improve oxygen transport immediately after transfusion without any need for cardiorespiratory compensation.

Acknowledgment

We want to thank Dr. Lloyd Dillingham, University of Washington egional Primate Center, Seattle, Washington, for providing us with some f the units of baboon red cells.

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Comparison of Filtering Efficiency of Four New In-line Blood Transfusion Filters

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Efficient removal of debris from stored human blood prior to transfusion has become increasingly important. The debris, consisting largely of microaggregates of platelets and fibrin, is not effectively removed by passage through a standard transfusion filter. This study evaluated the performance of four of the currently available small pore in-line blood transfusion filters. Filters tested included the Bentley PF-127, the Pall Ultipor SQ-40, the Swank In-Line IL-200 and the Fenwal Microaggregate Blood Filter. A standard blood administration filter was also tested, the McGraw V-2950. The rate of blood flow through the filters was recorded using single and multiple units of blood. The screen filtration pressure and debris weight of the filtered blood were studied to compare effectiveness of filtration. The Swank filter was effective in debris removal and maintained good flow rates. The Bentley and Fenwall filters removed debris nearly as well, but had reduction of flow rates after smaller infusions. The Pall filter maintained high flow rates but did not remove debris as effectively, particularly with pressure infusion. The standard 170 μ pore blood transfusion filter does not remove microaggregates.

INTEREST in more effective in-line filtration of blood prior to transfusion has been generated by recognition of the presence of microaggregate material which develops during the period of blood storage.[1,2,3,8,10] This "debris" consists principally of aggregates of platelets and fibrin.[1,3–6,8,10,11] Recent reports suggest that blood debris plays a role in the pathogenesis of post-traumatic pulmonary insufficiency.[2,6,7,9]

Several new in-line filters have been recently developed to remove these particulate microaggregates from banked blood. This study was undertaken to evaluate four commercially available filters, comparing their effectiveness in removing debris, the volume of blood that each can filter and the flow rates that can be maintained through each filter.

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Materials and Methods

The filters compared include: 1) standard blood administration filters (V-2950, McGraw Laboratories, Division of American Hospital Supply Corporation, Glendale, California); 2) the Bentley Disposable Infusion Blood Filter (PF-127, Bentley Laboratories, Inc., Irvine, California); 3) the Pall 40 μ Ultipor Disposable Blood Filter (SQ-40, Pall Corporation, Glen Cove, Long Island, New York); 4) the Swank In-Line Blood Transfusion Filter (IL-200, Pioneer Filters, Inc., Beaverton, Oregon); and 5) the Fenwal Microaggregate Blood Filter (Fenwal Laboratories, Division of Travenol Laboratories, Morton Grove, Illinois).

Units of outdated (21–23-day old) banked human blood were obtained from the Blood Bank of Hawaii. Blood had been collected in CPD bags and stored at 4 C. All units of blood were gently agitated by hand prior to the testing procedure.

From each bag 400 cc of blood was filtered through the test filters in 100 cc increments. Experiments using either single units (400 cc) or multiple units of blood (up to 1600 cc) were performed. Filters were tested with gravity flow and with flow generated by constant pressure of 150 mm Hg using a pressure infusion bag (Fenwal). The number of experiments with each type of filter are shown in Table 1 and the volume of blood filtered through each filter can be seen in Fig. 1.

All blood passed first through a standard blood administration filter then through the test filter and through a 2-inch length of ¼-inch diameter silastic tubing into a

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TABLE 1. *Number of Filters Tested*

	Swank	Bentley	Fenwal	Ultipor	Standard In-Line
Single Units (400 cc in 100 cc increments)					
Gravity	8	5	—	8	2
Pressure	8	8	—	8	2
Multiple Units (Up to 1600 cc in 100 cc increments)					
Gravity	4	3	2	3	0
Pressure	3	3	2	3	0

100 cc graduated cylinder. A stop watch was used to time each 100 cc flow.

Ten cc of unfiltered blood was obtained from each bag of blood for baseline studies of Screen Filtration Pressure (SFP) and Debris Weight (DW) by previously described techniques.[6] From each 100 cc of filtered blood, 10 cc was drawn into a syringe for measurement of SFP and DW.

Results

Every bag of stored blood used in the tests had accumulated significant amounts of debris, with a high debris weight and a control SFP near or exceeding 500 mm Hg. Flow rates are shown in Fig. 1 and post-filtration debris weights and screen filtration pressure in Figs. 2 and 3 respectively. Flow rates through the standard blood administration filter were high (Fig. 1). The standard filter did not significantly alter DW or SFP (Figs. 2 and 3).

The Ultipor filter allowed the highest flow rates which were sustained even with gravity filtration of as many as four units of blood (Fig. 1). The Ultipor was less effective in removing debris than either of the other three test filters (Figs. 2 and 3).

Flow rate was slightly lower initially with the Bentley, Swank and Fenwal filters; however, flow rates were adequately maintained through the Swank filters (50 cc/min.) even after three units of blood under gravity flow (Fig. 1). Gravity feed through the Fenwal and Bentley filters resulted in markedly reduced flows after less than two units of blood (Fig. 1). The Bentley, Fenwal and Swank filters were about equally effective in removing debris from the blood (Figs. 2 and 3).

Pressure infusion of the blood increased the capacity of all the filters in terms of the volume of blood that could be filtered at adequate flow rates (Fig. 1). Both the Ultipor and Swank filters maintained comparable flow rates after 1600 cc of blood. The Fenwal and Bentley filters showed flow rates significantly reduced after two or three units (Fig. 1). The Swank, Fenwal and Bentley filters maintained their efficacy in debris removal (Figs. 2 and 3). The Ultipor filter demonstrated decreasing effectiveness of debris removal after filtering three units of blood under pressure.

Discussion

Considerable evidence now exists that microaggregate material in banked blood is a significant factor in the development of post-traumatic pulmonary insufficiency. It has been shown that this debris can be effectively removed from banked blood by inline filtration with small pore filters.[6,11,12]

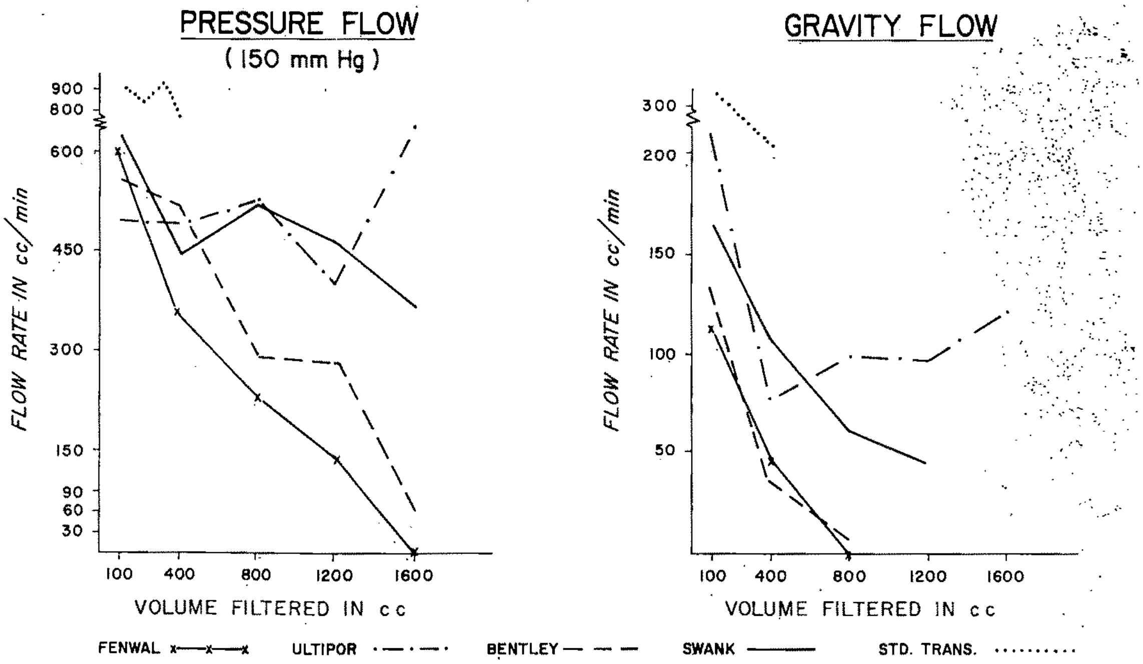

FIG. 1. Flow rates of in-line transfusion filters. Points represent the mean flow rates for the final 100 cc of the 400 cc filtration between points.

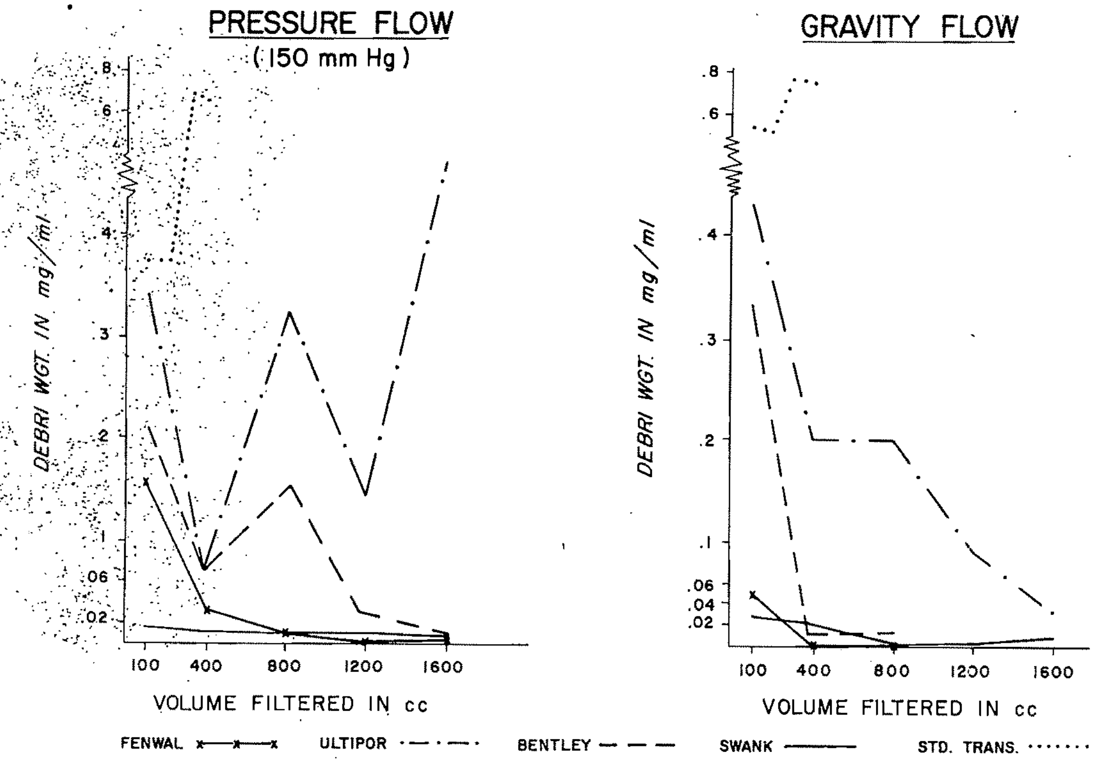

FIG. 2. Debris weights (DW) after in-line filtration. Points represent the mean debris weights for samples from the final 100 cc filtration between points.

The blood debris weights and SFP in Figs. 2 and 3 were done following passage of blood through various test filters. The standard blood transfusion filters have a pore size of 170 μ, which allows microaggregates to pass through as shown in Fig. 3. Microaggregate debris particles range in size from 10 to 150 μ.[10] The Ultipor filter is a surface filter made up of a polyester mesh with a 40μ pore size. The Bentley filter combines a surface filter polyester screen and a depth filter of polyester urethane foam. The Swank filter is a depth filter made up of packed dacron fibers. The Fenwal is a combination of screen, reticulated pore and compressed fiber depth filter. The Swank and Fenwal filters each have an elevated screen situated to block passage of larger clots prior to contact with the fine pore compressed fiber. In evaluating filters for clinical blood transfusion, a number of interrelated

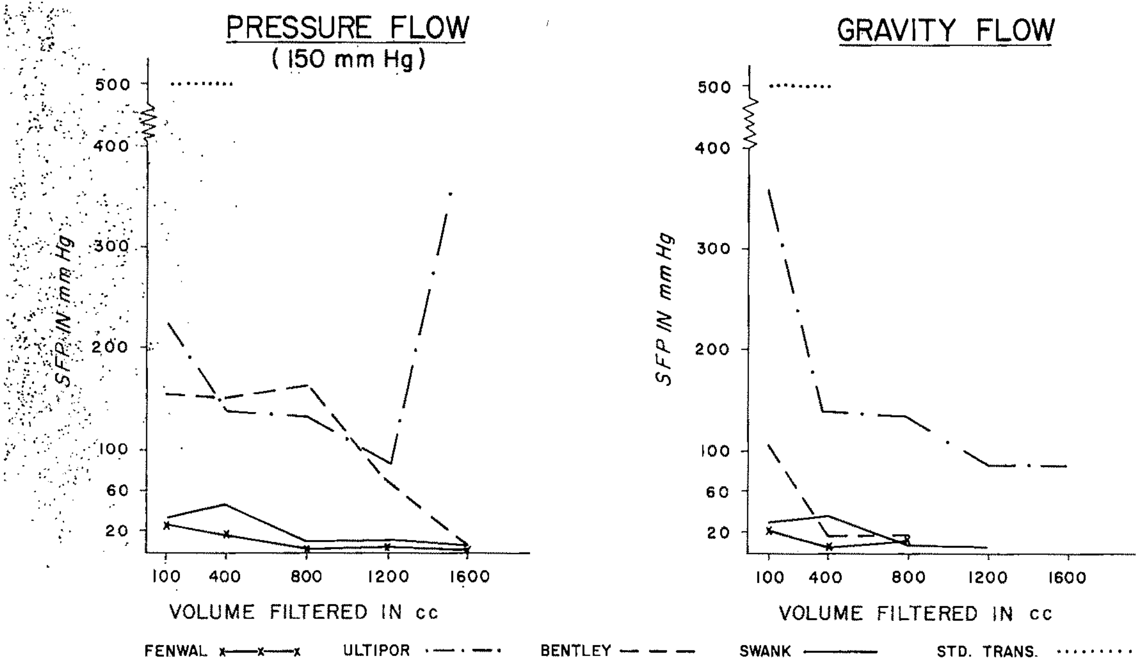

FIG. 3. Screen filtration Pressure (SFP) after in-line filtration. Points represent the mean SFP for samples from the final 100 cc of the 400 cc filtration between points.

factors must be considered included efficacy of debris removal, the volume capacity of each filter and the effect of pressure infusion on both flow and filter efficacy.

Based on the present study, the Pall filter is significantly less effective in removing debris, has a large filter capacity and becomes even less effective with blood infusion under pressure. The Bentley filter is effective in removing debris, maintains this effectiveness with pressure infusion, but has a significantly smaller filtering capacity (flow rate). The Fenwal filter is effective in debris removal but also had reduced flow rate. The Swank filter is effective in debris removal, maintains this effectiveness with pressure infusion and maintains adequate flow rates with pressure or gravity infusion. Based on these studies, the Swank filter appears superior to any of the others studied.

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The Association of Parathyroid Adenoma and Non-medullary Carcinoma of the Thyroid

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Thyroid carcinoma was discovered in five of 56 (8.9%) patients operated upon for hyperparathyroidism. In only one instance was a mass palpated preoperatively. An additional 26% of the 56 patients had either multinodular goiter or follicular adenomas. It is thus important to biopsy the thyroid nodules which may represent malignancy.

THE ASSOCIATION of parathyroid adenoma with medullary carcinoma of the thyroid and pheochromocytoma is well defined. Less well known is the association of papillary and follicular adenocarcinoma of the thyroid with parathyroid adenoma. In reviewing our experience with parathyroid adenomas, we encountered five such cases which we submit with a review of the experience of others.

Ogburn and Black, in 1956, reported one case of papillary carcinoma and three cases of mixed papillary and follicular carcinoma of the thyroid associated with parathyroid adenoma in a series of 230 cases of hyperparathyroidism.[5] Three of the four were operated primarily for parathyroid adenoma. On physical examination two had a single thyroid nodule and one had a multinodular goiter. The relationship was thought to be no more than coincidental. Ellenberg *et al*, in 1962, added seven patients with this association in a series of 93 patients with hyperparathyroidism (7.5%).[1] Pathologically, there were five papillary, one mixed papillary and follicular and one follicular adenocarcinoma. Trout and Mulder, in 1972, reported three cases of follicular adenocarcinoma in a series of 30 cases of hyperparathyroidism.[8] Krementz *et al.*, in reviewing 100 cases of hyperparathyroidism, found six unsuspected carcinomas of the thyroid.[4] There were two papillary, two follicular, and one sclerosing carcinoma and one gland had a medullary and Hurthle cell carcinoma in the same gland. Kaplan *et al.*, in an autopsy study, found four cases of parathyroid adenoma and thyroid carcinoma in 62 cases.[3] In 104 patients undergoing neck exploration for hypercalcemia, five unsuspected thyroid carcinomas were encountered. The pathological types were not mentioned; however, no medullary carcinomas were found.

In reviewing our experience with hyperparathyroidism at the University Hospital and the Veterans Administration Hospital, we too encountered a seemingly disproportionate number of unsuspected thyroid carcinomas (Table 1). Four were papillary adenocarcinomas and one was a follicular adenocarcinoma. Only one patient was found to have a neck mass preoperatively. The follicular adenocarcinoma was discovered when a small tissue sample from the fat at the lower pole of the thyroid was sent for a frozen section examination. The diagnosis was metastatic follicular adenocarcinoma to a lymph node. No masses were found in the thyroid and serial sections were done to find the primary. This was the only case where metastatic disease was encountered. In none was there an association with the degree of hypercalcemia or with duration of symptoms. Three were diagnosed on routine screening. The average age was 52 years and there were four females and one male. All have been followed in our clinics, on thyroid supression therapy and with no evidence of recurrent disease.

In addition, five of our patients were found to have single or multiple follicular adenomas (9%). Nine patients had multinodular colloid goiters (16.9%). One patient (L.G.) had two follicular adenomas in addition to a papillary adenocarcinoma. One patient had lymphocytic thyroiditis. These findings are in accordance with those of others.[3,4,8]

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† Professor and Chairman.

TABLE 1. *Authors' Experience with Hyperparathyroidism at the University Hospital and the Veterans Administration Hospital*

Patient	Age	Sex	Race	Parathyroid Pathology	Thyroid Pathology	Neck Mass	Duration of Symptoms
D.M.	55	F	B	Single chief cell adenoma	Papillary adenocarcinoma	No	Six years
L.L.	40	F	W	Single adenoma	Bilateral papillary adenocarcinoma	Yes	Eight months
W.B.	50	F	B	Single adenoma	Metastatic follicular adenoma (nodal metastases)—two follicular adenomas	No	None SMA-12 diagnosis
L.G.	53	F	W	Single adenoma	Papillary adenocarcinoma two follicular adenomas	No	SMA-12 diagnosis
T.L.	62	M	W	Single adenoma	Papillary adenocarcinoma	No	None SMA-12 diagnosis

Case Reports

D.M., a 55-year-old white female, presented here in May, 1964, with a four-year history of nephrolithiasis and pyelonephritis. She did not have a neck mass but had a serum calcium level of 12.3 mg% and a phosphorus of 1.8 mg%. She refused a neck exploration at that time. In April, 1966, she underwent a neck exploration in another state, where two normal parathyroids were removed, along with partial excision of a normal thyroid. She returned to our University Hospital in November, 1970, where subtotal thyroidectomy was performed for papillary adenocarcinoma without node involvement. Subsequent mediastinal exploration disclosed a chief cell parathyroid adenoma.

L.L., a 40-year-old white female, presented in January, 1971, with an eight-month history of a left neck mass and dysphagia. She, too, had a three-year history of nephrolithiasis. Her serum calcium level was 10.7 mg% and a phosphorus of 3.4 mg%. At operation she was found to have a parathyroid adenoma and several thyroid nodules. Frozen section analysis of thyroid tissue disclosed papillary adenocarcinoma bilaterally, and a left total and right subtotal thyroidectomy was performed. There was almost complete involvement of the left lobe, with capsular invasion but without demonstrable vascular involvement. The right lobe contained cystic adenocarcinoma.

W.B., a 50-year-old black female, presented in July, 1972, with cholelithiasis and was found to have a serum calcium level of 12.7 mg%, and a phosphorus of 2.4 mg% on a routine SMA-12. There were no neck masses. At neck exploration she was found to have a left upper pole parathyroid adenoma (800 mgm). The thyroid gland was grossly normal, but a left lower pole nodule, submitted as a possible parathyroid adenoma, was found on frozen section to be metastatic follicular adenocarcinoma of the thyroid. She underwent a left total and a right subtotal thyroidectomy. Permanent sections revealed a non-encapsulated follicular adenocarcinoma on the left lower lobe with venous and lymphatic invasion. One of five lymph nodes were positive. Incidentally, two small follicular adenomas were found in the left upper and right upper poles, respectively.

L.G., a 53-year-old white female, presented in July, 1972, with low back pain. Physical examination was unrevealing and a routine SMA-12 revealed a serum calcium level of 11.8 mg% and a phosphorus of 3.6 mg%. Intravenous pyelogram, long bone survey and thyroid scan were normal. Neck exploration was carried out and a parathyroid adenoma was found near the right lower pole. Subtotal thyroidectomy was performed because the gland contained multiple nodules. Permanent sections revealed a 3 mm well-differentiated papillary adenocarcinoma which was partially encapsulated. No capsular invasion was demonstrated. In addition, there were two encapsulated follicular adenomas and several colloid nodules.

T.L., a 62-year-old white male, presented in July, 1969 with an SMA-12 finding of persistent hypercalcemia, the serum calcium level being 11.5 mg% and phosphorus was 1.7 mg%. The neck examination was negative. At operation a 5.5 gm parathyroid adenoma was found at the left lower lobe of the thyroid gland. The right thyroid lobe contained a nodule which was resected, resulting in a diagnosis of papillary adenocarcinoma.

Discussion

The role of calcium as a goitrogen is well defined in the experimental animal.[7] The development of thyroid neoplasms in rats and mice on the goitrogen thioarea have been described.[2,6,7] The notable incidence of goiter, follicular adenomas and thyroid carcinomas in association with parathyroid adenomas leads to speculation that they are causally related. It is interesting that two of our patients had two discrete follicular adenomas in addition to thyroid adenocarcinomas.

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Intra-aortic Balloon Counterpulsation:

Potential for Therapy in Hemorrhagic Shock with Associated Myocardial Failure

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After attaching appropriate monitoring devices enabling the measurement of the slope of the left ventricular function curve, left atrial pressure, mean aortic pressure, peak left ventricular pressure, and tension time index, three groups of ten dogs were subjected to varying periods of hemorrhagic shock until a slope of their ventricular function curve was reduced to either 75% (Group I), 50% (Group II), or 25% (Group III) of their baseline value. Resuscitation was attempted in all dogs by the intravenous infusion of shed blood plus additional balanced salt solution. This infusate was administered to maintain either the mean aortic pressure within 15 mm Hg of the baseline value or a left atrial pressure of 15 mm Hg, whichever occurred first. One half of the dogs received, in addition, intra-aortic balloon counterpulsation. All dogs not receiving counterpulsation expired within two hours. There was no apparent effect of counterpulsation on Group I animals. Three of five animals (Group II) and four of five animals (Group III) receiving counterpulsation survived to the end of the experiment with significant ($p < .01$) improvement in the parameters monitored. The utilization of counterpulsation as an adjunct to treatment in hemorrhagic shock is suggested.

IN RECENT YEARS the principle of counterpulsation has been an increasingly attractive approach to supporting an injured and failing myocardium. Specifically, intra-aortic balloon counterpulsation (IABC) is an effective method of compensating for myocardial failure following myocardial infarction.[5,8,9,14] This investigation was undertaken to evaluate the potential role of IABC as a therapeutic modality in myocardial failure following hemorrhagic shock.[1,2,7,10]

It seemed necessary to determine if the potential degree of support offered by IABC to the failing heart was a function of the severity of the failure. In this investigation, three different degrees of myocardial failure were created in animals to determine the quantitative improvement in myocardial function associated with IABC and to relate that improvement to improved survival.

Methods

Preparation of Animals

Mongrel dogs in excess of 20 kg were utilized. After anesthetization with pentabarbital sodium, all animals were intubated and connected to a Harvard respirator. A median sternotomy with attachment of an electromagnetic flow probe,[°] pressure monitoring cannulas, and insertion of a counterpulsation balloon[†] in the descending thoracic aorta were then performed as illustrated in Fig. 1. This preparation enabled the continuous monitoring of right atrial pressure (RAP), left arterial pressure (LAP), left ventricular pressure (LVP), peak left ventricular pressure (PLVP), mean aortic pressure (MAP), cardiac output (CO) and the calculation of peripheral vascular resistance (PVR). Tension time index (TTI) was approximated by integrating the area beneath the left ventricular pressure curve. A pump-oxygenator circuit as illustrated in Fig. 1 facilitated the infusion of oxygenated blood into the left atrium and enabled the construction of the slope of the left ventricular function curve by plotting change in left atrial pressure against

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[*] Jefferson-Pilot Research Fellow.

[°] Carolina Medical Electronics.

[†] Westinghouse Model IV Counterpulser, Avco Balloon.

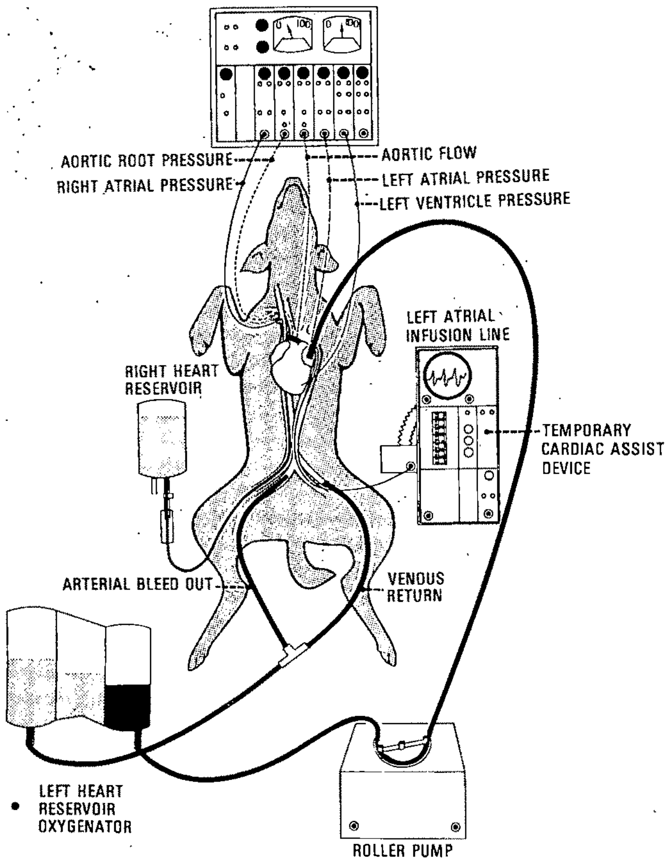

FIG. 1. Diagramatic illustration of the experimental preparation.

change in cardiac output. (Moseley Autograph, Model 2050 AM X-Y Recorder).

Experimental Design

Three groups of ten dogs were studied. After preparation of the animals and collection of baseline data as described above, an oxygenated mixture of whole blood and balanced salt solution was infused into the left atrium for ten seconds at a flow rate of 10 ml/sec, and the slope of the resulting baseline left ventricular function curve was noted.

All animals were bled through their arterial cannula until the MAP was reduced to 40 mm Hg. The measurements described above were successively repeated at 30-minute intervals. MAP was maintained at 40 mm Hg by intermittent infusion or withdrawal of blood until a specific degree of left ventricular failure was achieved as measured by a reduction in the slope of the left ventricular function curve when compared with the baseline slope. The three groups were reduced respectively to: Group I, 75%; Group II, 50%; and Group III, 25%.

After the desired degree of myocardial failure was achieved in each group, a mixture of shed blood plus balanced salt solution was infused intravenously until either the MAP returned to within 15 mm Hg of the baseline value or until the mean LAP reached 15 mm Hg. If left atrial pressure reached 15 mm Hg before mean aortic pressure was within 15 mm Hg of the baseline value, the infusion was discontinued until left atrial pressure had decreased to 10 mm Hg, at which point infusion resumed. The measurements described above were then repeated. After these measurements, each group of ten dogs was alternately divided into two sub-groups of five. One sub-group received only intermittent volume restoration in an attempt to maintain mean aortic pressure within 15 mm Hg of baseline, while the other sub-group received continuous IABC in addition to intermittent volume infusion. Measurements were continued at 30-minute intervals in all animals for four hours or until the death of the animal.

Results

The Quantitative Effect of IABC

The effect of IABC on those parameters describing left ventricular performance is depicted in Table 1. These data were collected immediately after initial volume restoration and compares animals with and without IABC. Utilizing a paired t test, it was shown that in the group with the most myocardial failure (Group I), IABC had no statistically significant effect ($p > .01$) in terms of the parameters monitored. One animal in Group I expired during the shock period. In both Groups II and III a significant ($p < .01$) improvement was noted for all parameters with the exception of TTI in Group II and TTI and PLVP in Group III. PLVP was significantly ($p < .01$) increased in Group II.

Comparison of the data collected from Groups II and III does not seem to indicate any significant quantitative difference in the magnitude of the response to IABC for these groups.

The Effect of IABC on Survival

Group I. It required from three to five hours of MAP = 40 mm Hg to achieve a 75% reduction in the slope of the ventricular function curve. It is evident from Table 1 that neither the infusion of intravenous fluid alone nor infusion of fluid in conjunction with IABC was capable of fully restoring any parameter to its baseline value. As might be expected from this lack of response to IABC on the part of Group I animals, there was no prolongation of life noted in conjunction with IABC, death occurring in all animals in both sub-groups by 90 minutes after the end of the shock period.

Group II. It required 2½–4 hours of MAP = 40 mm Hg to achieve a 50% reduction in left ventricular function. As noted in Table 1, IABC had a significant effect upon left ventricular performance. This effect appears to be sustained for two to three hours and was associated with improved survival (Fig. 2).

All but one animal not receiving IABC support expired

TABLE 1. *Response to IABC for Three Degrees of Myocardial Failure*

		Baseline	$\bar{s}$ IABC	$\bar{c}$ IABC	p
Group I (75% slope)					
MAP	$\bar{x}$	105	21.6	20.2	
	s.e.	3.63	8.18	6.33	>.01
	n	4	4	4	
LAP	$\bar{x}$	5.5	16.3	15.8	
	s.e.	2.83	2.53	2.86	>.01
	n	4	4	4	
CO	$\bar{x}$	3.25	.44	.38	
	s.e.	.93	.19	.22	>.01
	n	4	4	4	
PLVP	$\bar{x}$	142.8	41.3	40.1	
	s.e.	9.65	6.28	5.35	>.01
	n	4	4	4	
TTI	$\bar{x}$	96.6	62.5	68.6	
	s.e.	8.25	4.33	8.69	>.01
	n	4	4	4	
Group II (50% slope)					
MAP	$\bar{x}$	98.6	28.7	50.6	
	s.e.	4.46	5.37	4.75	<.01
	n	5	5	5	
LAP	$\bar{x}$	6.9	14.9	8.7	
	s.e.	1.92	1.85	1.02	<.01
	n	5	5	5	
CO	$\bar{x}$	2.21	.63	1.41	
	s.e.	.57	.16	.39	<.01
	n	5	5	5	
PLVP	$\bar{x}$	133.6	52.8	78.2	
	s.e.	8.17	6.82	3.51	<.01
	n	5	5	5	
TTI	$\bar{x}$	83	34.8	49.5	
	s.e.	7.89	5.37	6.89	<.01
	n	5	5	5	
Group III (25%) slope)					
MAP	$\bar{x}$	101.5	38.3	65.5	
	s.e.	5.13	4.28	5.01	<.01
	n	5	5	5	
LAP	$\bar{x}$	7.8	10.3	8.7	
	s.e.	1.35	1.2	.99	<.01
	n	5	5	5	
CO	$\bar{x}$	2.06	.86	1.95	
	s.e.	.46	.13	.41	<.01
	n	5	5	5	
PLVP	$\bar{x}$	146.2	59.3	68.2	
	s.e.	9.25	7.15	2.88	>.01
	n	5	5	5	
TTI	$\bar{x}$	75.1	30.8	35.2	
	s.e.	8.33	4.80	7.25	>.01
	n	5	5	5	

Data are presented as mean ($\bar{x}$), standard error (s.e.) and number of animals (n).

within one hour, and the remaining animal expired two hours after the end of the shock period. All animals in the IABC sub-group survived more than three hours and three survived beyond four hours. It is apparent that animals receiving IABC fared better than those in the non-IABC sub-group. The slope of the left ventricular function curve was significantly ($p < .01$) improved by IABC. Despite the prolonged survival and improved left ventricular performance, neither intra-venous infusion alone nor infusion in conjunction with IABC was able to restore the parameters monitored to their baseline value. Deterioration in the slope of the left ventricular function curve appeared to be delayed by IABC.

Group III. A 25% reduction in left ventricular function was achieved after 2–3½ hours of MAP = 40 mm Hg. As in Group II, a sustained improvement in left ventricular function was noted in the IABC sub-group (Fig. 3). This was associated with prolonged survival, with four of five animals surviving beyond the four hour experimental period. The severity of the preparation is illustrated by the failure of any animal in the non-IABC sub-group to survive beyond one and a half hours.

Of particular interest is the single death in the IABC subgroup. This death occurred in conjunction with stopping counterpulsation to change compressed gas cylinders. During this ten minute period the mean aortic pressure decreased from 65 mm Hg to 20 mm Hg, cardiac output decreased from 1.25 L/min to less than .20 L/min, left atrial pressure rose from 10 to 14 mm Hg, and the animal expired, illustrating the dependence upon the counterpulser to maintain cardio-vascular dynamics.

Although not demonstrated by the mean data (Table 1), mean aortic pressure and cardiac output were restored to their baseline values in three of the five animals utilizing IABC plus intravenous infusion; whereas, this was not accomplished by the infusion of fluid alone.

It is evident from Figs. 2–4 that the overall course of all animals in Groups II and III receiving IABC was nearly identical. There was no improvement in TTI and PLVP in either Group II or III (Fig. 4). This was confirmed by screening the data with multiple t tests. No significant ($p > .01$) difference was noted and further statistical analysis did not seem warranted.

Discussion

In this study the effect of IABC was evaluated in three degrees of myocardial failure referenced to the baseline slope of the left ventricular function curve. The significance of this approach is that the variability between animals can be reduced. Note that in each of the three groups a variable amount of time was needed to achieve the same degree of myocardial impairment. The ability to restore ventricular performance in this study can be assumed to be a function of the efficiency of the IABC system, the limitations imposed upon left ventricular performance by a failing right heart, alterations in pulmonary vascular resistance, and the degree of left ventricular failure present.

The lack of effect noted in Group I suggests that with extended myocardial deterioration due to hemorrhagic shock IABC has little if any potential benefit. The data from

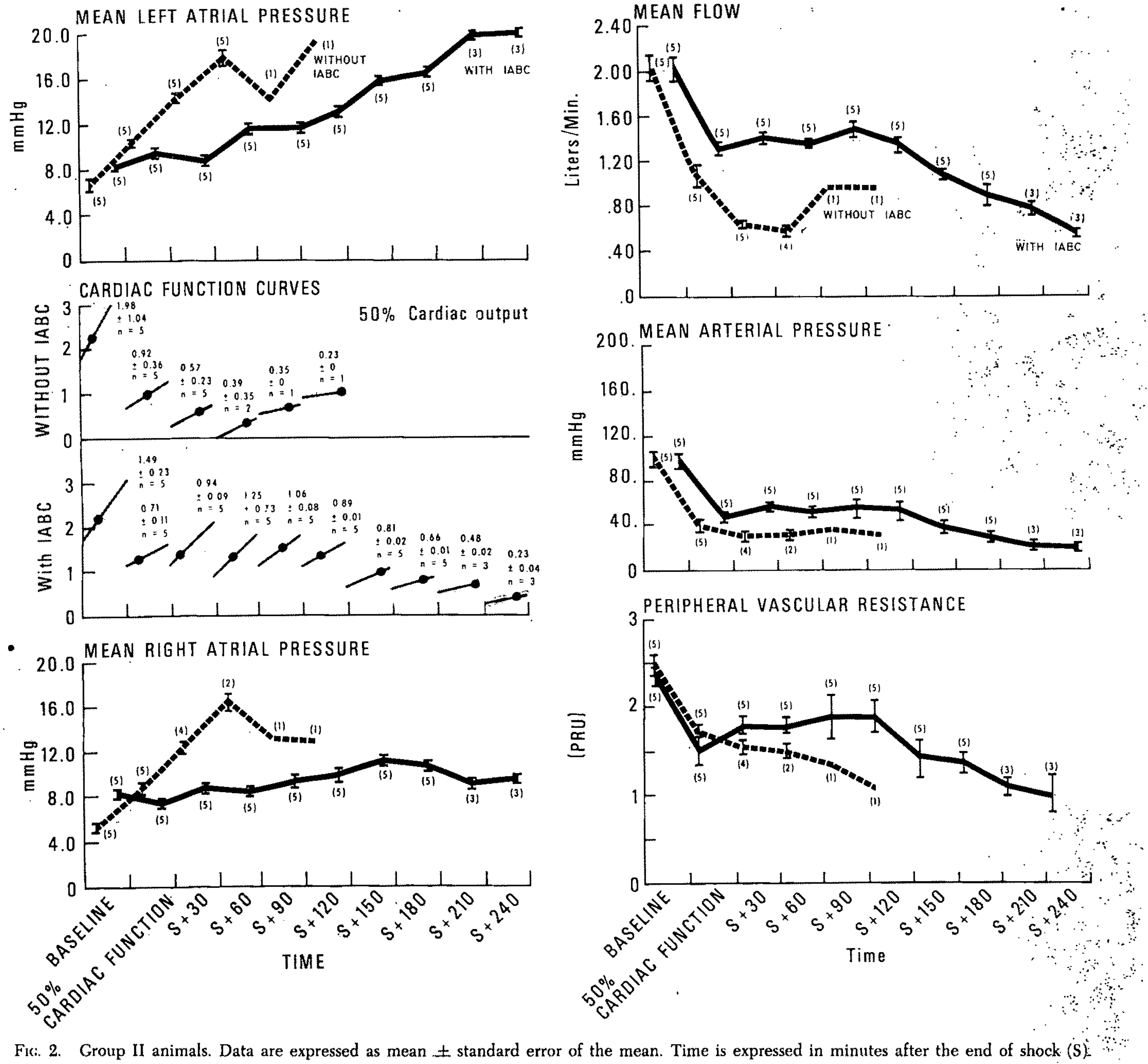

FIG. 2. Group II animals. Data are expressed as mean ± standard error of the mean. Time is expressed in minutes after the end of shock (S).

Groups II and III indicate approximately an equal quantitative improvement in ventricular performance when IABC was instituted in the presence of a 25–50% reduction in ventricular function. This improvement was sufficient to allow restoration of cardiac output and mean aortic pressure to baseline in three of the five animals in Group III, and resulted in prolongation of life in seven of ten of the animals in Group II and III receiving IABC.

Our previous work[6] in which we noted very little effect of IABC when utilized in conjunction with a non-failing myocardium in the dog, along with the data collected in this study, imply that IABC is most effective for a range of 25–50% reduction in myocardial performance. This varied response along with differences in survival associated with clinical trials of IABC,[3,9,12] raise the question as to whether selection of patients for IABC by assessment of ventricular function might improve results.

A failure to reduce tension time index and peak left ventricular pressure in Groups II and III was noted. This is an indication that continued metabolic work on the part of the myocardium was not reduced by IABC.[11] In view of the improvement in all other parameters and the prolongation of

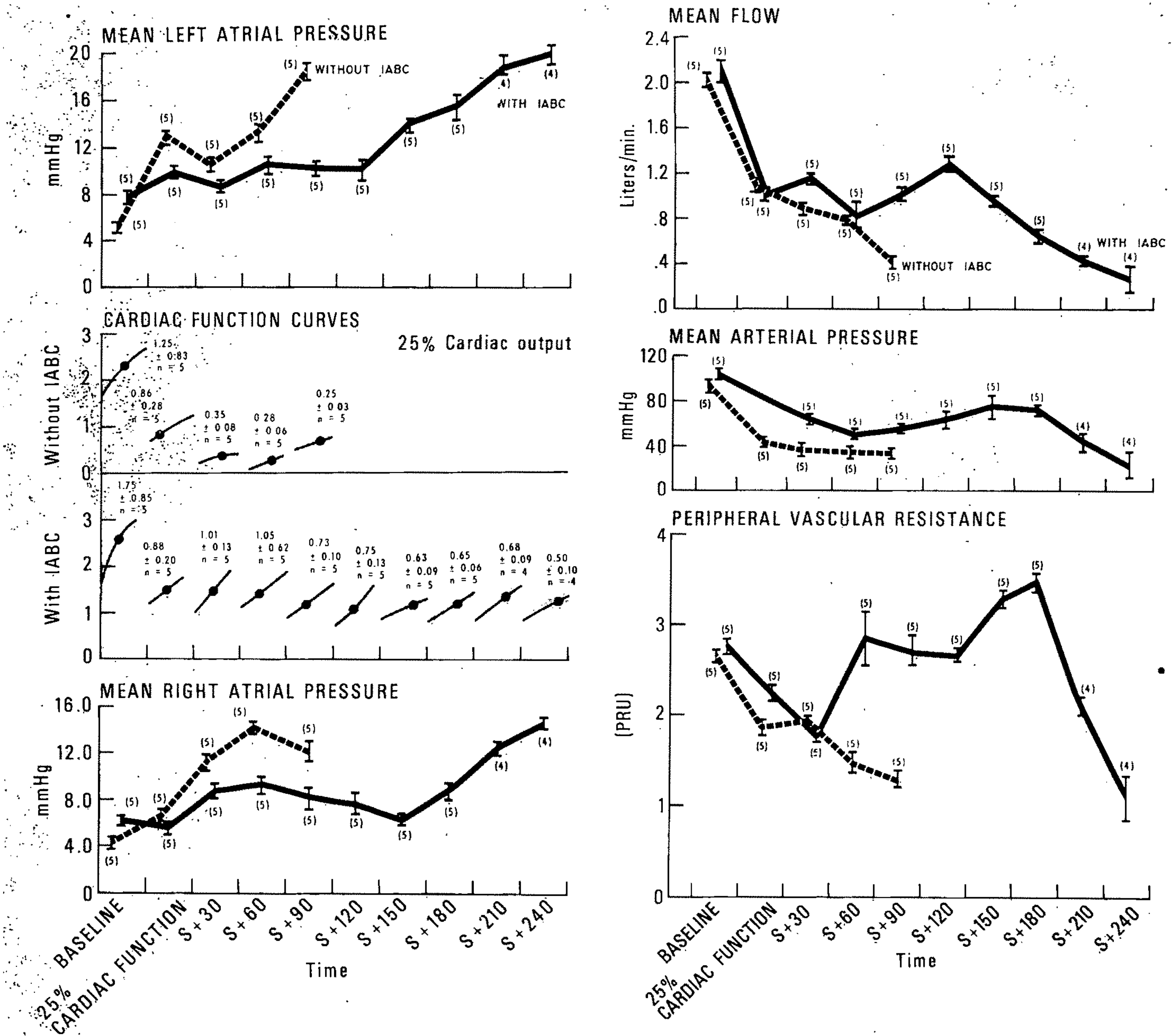

FIG. 3. Group III animals. Data are expressed as mean ± standard error of the mean. Time is expressed in minutes after the end of shock (S).

survival associated with IABC, it is unlikely that this is a reflection of improper balloon timing. Rather, we believe that IABC resulted in a healthier myocardium capable of more work, (perhaps through increased perfusion) with this effect being more evident than any decrease in afterload achieved by IABC.

The principle of IABC treatment rests squarely on the assumption that the myocardial tissue damage can be limited and/or restored during IABC. The data show evidence supporting this assumption. In Groups II and III the institution of IABC dramatically changed the rate of decline of left ventricular function (Figs. 2 and 3), and caused reversal of the slope toward a normal value for a period of time.

All animals remained balloon dependent during the four hours of this study as evidenced by the short survival of the non-IABC animals and the one death in the Group III IABC sub-group.

Formal data collection ended after four hours; however, animals with IABC frequently lived on for an additional two hours. In view of the total time for the experiment, the magnitude of the surgical preparation, and the fact that no attempt was made to control arterial pO_2 and acid base status, it is evident that other factors played a contributory role

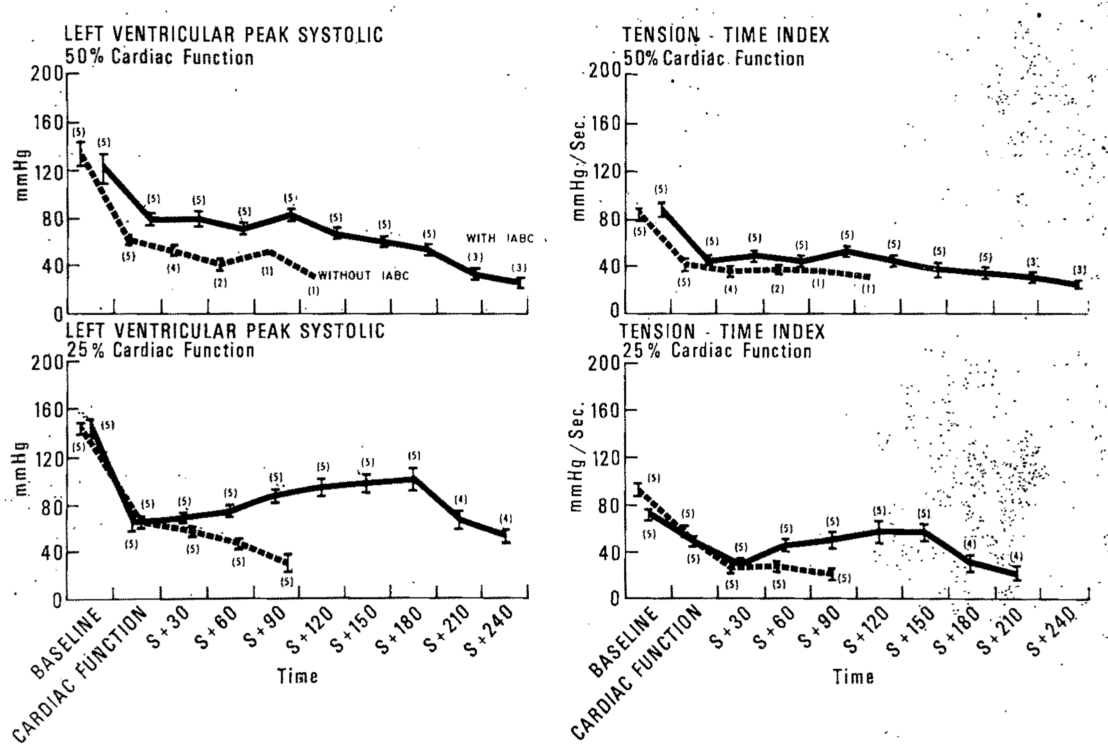

FIG. 4. Mean and standard error of the mean for Groups II and III. Note lack of improvement in LVPS and TTI in both groups.

in the eventual demise of the animals. Terminally, the limiting factor in all animals appeared to be the inability to sustain an adequate mean aortic pressure and presumably an adequate coronary perfusion. The role of peripheral vascular collapse in death following hemorrhagic shock has been presented by others.[4,13,15]

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Mesenteric Thrombosis Following Splenectomy

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Three cases of postsplenectomy mesenteric thrombosis, two associated with thrombocytosis, are presented. Experience has shown that persistent thrombocytosis, accompanied by abnormal platelet function, is not a benign condition and may be associated with thrombosis. When encountered, postsplenectomy thrombocytosis of greater than 800,000 per mm^3 must be evaluated by platelet function studies and anticoagulation begun. Post-prandial cramping abdominal pain may be an early symptom of thrombosis, demanding immediate anticoagulation. Low-dose heparin, ASA, and dipyridamole are three of the more commonly used treatment modalities. Small bowel resection is indicated if thrombosis occurs.

MESENTERIC VEIN THROMBOSIS following splenectomy is a rare but often fatal complication which may be related to thrombocytosis. Normal platelet counts (140,000–440,000 per mm^3) routinely will increase 30–100% following splenectomy, usually reaching a maximum 7–20 days postoperatively.[12] Postsplenectomy mesenteric thrombosis usually has been accompanied by platelet counts in excess of 600,000–800,000 per mm^3[3,4,5] contributing to a postoperative hypercoagulable state. Signs, symptoms and sequelae for three patients with postsplenectomy mesenteric thrombosis are presented, two of whom had platelets in excess of 1,300,000 per mm^3.

Case Reports

Case 1. A 26-year-old Puerto Rican dentist with a history of anemia since age 11 was found to have spherocytosis with hypersplenism and was referred for splenectomy. The spleen was not grossly palpable, and the remainder of the physical examination was unremarkable. His preoperative hemoglobin was 8.5 gm%, and his platelet count 399,000 per mm^3. On March 27, 1973, the patient underwent routine splenectomy and liver biopsy. Initially he did well, with a hemoglobin of 8.3 gm%, a white count showing the usual elevation to 25,000 per mm^3, and a platelet count of 515,000 per mm^3 on his first postoperative day. On his second postoperative day his platelets rose to 815,000 per mm^3, with hemoglobin and white count unchanged. Four days after surgery he was eating a regular diet, which he tolerated well. Two days later he complained of an inability to pass flatus and of postprandial abdominal distention. Supine and upright films of the abdomen showed distended loops of colon and small bowel, a nonspecific gas pattern, with no evidence of bowel obstruction. His platelet count was 1,325,000 per mm^3; serum amylase was normal.

Eight days after operation the patient's temperature rose from 100.2° to 104.6 F and his pulse rose to 240 beats/min. His blood pressure dropped from 120 to 60 mm Hg systolic. His hemoglobin had risen to 11.9 gm%, and his white count to 31,400 per mm^3. Supine and upright X-rays of the abdomen showed little small bowel gas, and less gas in the colon than on the previous day's study. The patient was resuscitated with multiple blood and colloid transfusions. An exploratory laparotomy a few hours later showed superior mesenteric venous thrombosis with arterial pulsations intact. Almost 100% of the small bowel was infarcted. This was resected, and a jejuno-right colostomy performed. He expired 36 hours later in irreversible shock, which was due to a combination of sepsis, hemorrhage, and "third space" fluid accumulation.

Immediately prior to surgery, the patient appeared to develop a consumptive coagulopathy, with platelets dropping to 95,000 per mm^3 (Fig. 1), a Lee-White clotting time of 18 min (normal 8–12 min), thrombin time of 21 sec (normal 12 sec), quantitative fibrinogen of 88 mg% (normal 170–410 mg%), and fibrinogen degradation products increased to a 1:20 dilution (normal 1:5 dilution).

Case 2. The patient, a 56-year-old gravida IV, para IV, was admitted June, 1970, for elective repair of vaginal prolapse. Routine preoperative evaluation showed a platelet count of 30,000 per mm^3. After hematologic evaluation, splenectomy was advised for her idiopathic thrombocytopenic purpura.

On June 24 her hemoglobin was 14.6 gm%, and her platelet count 42,000 per mm^3. She had an elective splenectomy and hiatus hernia repair on June 30, 1970. Initially she did well. However, two weeks postoperatively she began complaining of vague but generalized abdominal discomfort, especially after eating. An upper gastrointestinal series and barium enema showed no evidence of intra-abdominal abscess. On July 18 she experienced more intense abdominal pain, and her pulse increased to 130 beats/min. Supine and upright films of the abdomen were interpreted as showing ileus. She became progressively more distended; serous fluid was aspirated from her peritoneal cavity. At operation 2000 cc of serous fluid was aspirated and 62 cm of gangrenous bowel was found just distal to the ligament of Treitz. The gangrenous segment was resected, with a primary end-to-end anastomosis. Pathology reported hemorrhage in the mesentery,

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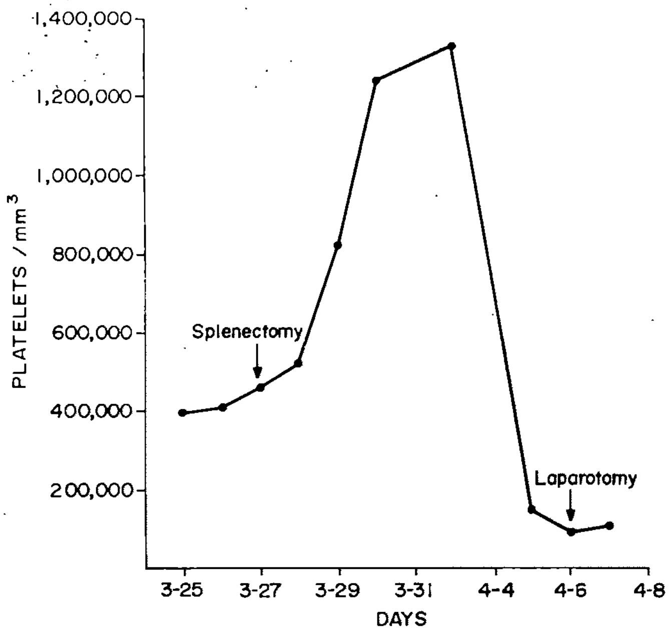

FIG. 1. Postsplenectomy thrombocytosis. Note drop in platelet count as patient developed a pattern of disseminated intravascular coagulopathy.

with inflammation and necrosis of the mesenteric veins. The arteries were intact. Postoperatively she was given heparin but still complained of mild abdominal pain after eating.

On July 25 the patient was unable to void, her abdomen became quite distended, and her pain increased. Twenty-five hundred cc of serosanguineous fluid was removed from her abdomen at emergency surgery, but no cyanotic or distended bowel was seen. Postoperatively she continued to have mild cramping abdominal pain, exacerbated by eating. On August 15 her pain increased in severity, and her pulse rose to 160 beats/min. Laparotomy revealed complete small bowel infarction with venous thrombosis. She died on the operating table.

Case 3. The patient, a 43-year-old white woman, was first noted to have an enlarged spleen at the time of a varicose vein stripping in 1959. In 1963, she was admitted because of progressive fatigue and epigastric fullness. Family history revealed that both parents had died of leukemia, and one brother was post splenectomy for myelofibrosis. The patient's platelet count was 1,175,000 per mm³, her hemoglobin 12.8 gm%, and her white count 8,100 per mm³. Myelofibrosis was diagnosed on the basis of a bone marrow biopsy, and she was started on Myleran and discharged. She was readmitted in February, 1967, with abdominal pain and difficulty in breathing. Splenomegaly was noted and splenectomy recommended. Platelet count at splenectomy was 1,325,000 per mm³. After routine splenectomy she was released on Myleran, with the discharge diagnosis of myelofibrosis with myeloid metaplasia.

The patient was readmitted three months later with vague abdominal pain, for which no etiology could be ascertained. She was found to have an enlarged liver and was discharged. She returned in June, two weeks later, with left epigastric pain, which was exacerbated by eating and relieved by passing flatus and moving her bowels. In September she developed upper gastrointestinal bleeding; massive hepatomegaly and esophageal varices were noted. Portal decompression was suggested, but at operation her portal venous pressure measured 55 cm H_2O, and both her middle colic and superior mesenteric veins were found to be thrombosed. A shunt was not performed, and her abdomen was closed. She was discharged two weeks later without complication.

She was readmitted six days later with massive esophageal bleeding. Esophageal varices were ligated, and a perforated duodenal ulcer was oversewn. On her twenty-first postoperative day she again perforated her ulcer, and died five days later. Postmortem examination showed portal vein thrombosis extending into the splenic and superior mesenteric veins, pulmonary embolus with infarction of the right upper lobe, and myelofibrosis with myeloid metaplasia of the liver.

Discussion

Historically, Rosenthal[10] first described postsplenectomy thrombocytosis in 1923, by classifying people with "Banti's syndrome," congestive splenomegaly, into two groups. One group had low to normal preoperative platelet counts but postoperatively experienced a tremendous rise, which remained elevated. This group had an increased incidence of generalized thrombosis and hemorrhage.

Miller and Hagedorn[8] reported a high complication rate in splenectomy for congestive splenomegaly. Four of 45 patients with cirrhosis of the liver developed thrombosis of splenic, superior mesenteric, portal or left gastric veins.

Barker and co-authors[1] found a high incidence of embolic and thrombotic complications following splenectomy, when compared to all other abdominal operations performed. Thrombophlebitis was second in incidence only to that following hysterectomy. Fatal and nonfatal pulmonary emboli, and all other emboli and thromboses, occurred most frequently following splenectomy.

In 1963 Hayes[4] reported three cases of systemic thrombocytosis. Two were post splenectomy for hemolytic anemia, and both had pulmonary emboli.

Bull, Zikria, and Ferrer,[3] in 1964, reported two cases of mesenteric thrombosis post splenectomy and reviewed the literature, finding two other cases.

In an attempt to uncover its etiology, Johnson and Bagenstoss[6] have described three major factors affecting vascular thrombosis: 1) alterations in blood composition, such as reticulocyte proliferation and increase in red cell hemolysate; 2) stasis of blood; and 3) injury to vessels. Thrombocytosis is the most common alteration in blood composition associated with splenectomy. Lipson and Bayrd[7] demonstrated thrombocytosis in 29% of 119 splenectomized patients. They found that patients with hemolytic anemia or agnogenic myeloid metaplasia displayed a high incidence of thrombocytosis, presumably on the basis of bone marrow stimulation. There are no other diseases for which splenectomy has consistently produced thrombocytosis and thrombosis. Since no relationship exists between pre- and postoperative platelet counts, it is difficult to predict which patients will have postoperative thrombocytosis. Hayes and Spurr[4] have proposed that postsplenectomy thrombocytosis is due to loss of important splenic properties such as: removal of senescent platelets; production of a humoral factor to stimulate or suppress bone marrow megakaryocytes; or a combination of both properties, thus allowing a build-up of platelets to occur.

Hirsch and Dacie[5] have found a close correlation between postsplenectomy anemia and thrombocytosis. They suggest that anemia stimulates thrombopoiesis as well as erythropoiesis, and that splenectomy in the face of pre-existing anemia may cause a persistent thrombocytosis.

Zucker and Mielke,[14] in a clinical study, divided thrombocytosis into three categories; all had similar platelet counts: 1) reactive thrombocytosis secondary to splenectomy; 2) asymptomatic thrombocytosis associated with myeloproliferative disease; and 3) symptomatic thrombocytosis with myeloproliferative disease, causing recurrent emboli, hemorrhage, or thrombosis. Bleeding time, platelet adhesiveness, and platelet aggregation response to ADP, epinephrine, and collagen were normal for patients in category 1, and mildly abnormal in category 2. All those in category 3 had absence of epinephrine-induced platelet aggregation, with resultant increased bleeding time. Platelet adhesiveness was decreased in this group, and epinephrine caused neither platelet aggregation nor activation of platelet factor III, responses which were normal in the other two groups. It was their opinion that the response of platelets to epinephrine could be used to differentiate those with high-risk thrombocytosis from those with asymptomatic thrombocytosis, at least in those with myeloproliferative disorders.

Treatment of postsplenectomy thrombocytosis remains a controversial topic. Some authors recommend anticoagulation routinely, many use anticoagulants only until the patient ambulates, while others anticoagulate routinely if the platelet count exceeds 800,000–1,000,000 per mm^3. Acetylsalicylic acid[13] and dipyridamole have been successfully used, while heparin,[11] in doses of up to 100 mg intravenously q 6 hr, has also become popular. The latter, in low doses, has been shown to prevent routine postoperative decrease in platelet aggregation to ADP.[9]

Chemotherapy, using 6-mercaptopurine, ^{32}P, Busulfan, and uracil mustard, has been effectively used for thrombocytosis associated with myeloproliferative diseases. In one clinical trial,[14] chemotherapy reduced platelet counts and incidence of pulmonary embolus in four out of five patients with symptomatic thrombocytosis. Recently, L-phenylalanine mustard has shown promise in the treatment of symptomatic postsplenectomy thrombocytosis, and in hemorrhagic thrombocythemia.[2]

Mesenteric thrombosis must be considered in any patient whose progress is slow post splenectomy. Vague, cramping abdominal pain, exacerbated by eating and relieved by passage of flatus or bowel movement, is a common symptom. Depressed bowel sounds, with abdominal distention and generalized abdominal tenderness, accompanied by dilated loops of bowel in an ileus pattern by X-ray, support the diagnosis. Tachycardia and low-grade fever, accompanied by a rising hemoglobin and white count, further support the diagnosis of mesenteric venous thrombosis, with massive loss of fluid into a "third space." Once thrombosis has occurred, immediate surgery offers the patient his only chance for survival. Since the advent of oral and intravenous hyperalimentation, many surgical triumphs have been made in massive gastrointestinal resection, and large segments of small bowel can be resected safely.

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Letters to the Editor

June, 1974

Dear Editor:

In the early part of his paper in the June 1974 issue of Annals of Surgery Dr. Clifford Herman states that the endotoxemia which has been demonstrated in the experimental animal in shock has not been demonstrated in man or the primate. There are no less than a dozen papers, some published in 1971 and 1972, demonstrating endotoxemia in man in a variety of non-septic as well as septic disorders. In any case, his experimental model for hemorrhagic shock misses the point at issue, which is to discover why hemorrhagic shock becomes refractory to transfusion. In the first group of seven baboons, six responded to transfusion and were therefore resistant to the degree of duration of hypovolemia imposed. Since the second group were not transfused, and cannot be assessed as either resistant or refractory to transfusion, he leaves the study where it began.

As for the role of endotoxemia in the development of the refractory state, he reports positive bloods early as well as late in shock in both groups. The finding of endotoxin early in shock is at odds with a number of other studies that yield uniformly negative results in this phase of hemorrhagic shock, and in any phase in resistant animals. It does appear in non-resistant animals, as we have reported, late in shock, but usually not until transfusion flushes it out of the gut where flow until then is almost at a standstill.

In a previous paper Dr. Herman reported positive bloods in the normal animal, a finding which those with extensive experience with the *Limulus* lysate test will not accept. This raises the question of technical errors in the assay.

My main purpose in writing this note is to suggest that Annals of Surgery consider a place for publishing responsible criticism from its readers.

Jacob Fine, M.D.
Harvard Medical
School
Dept. of Surgery

July, 1974

Dear Editor:

Thank you for the opportunity of responding to Dr. Fine's letter. Our first point relates to his comment that we have stated that "the endotoxemia which has been demonstrated in the experimental animal in shock has not been demonstrated in man or the primate." Our statement is really restricted to hemorrhagic shock. We intended to indicate only that there is a paucity of evidence of splanchnic ischemia and resultant endotoxemia in hemorrhagic shock in man or subhuman primates. With the indicated exception of the older patients with arteriosclerotic mesenteric vascular narrowing, we have found no published reports of endotoxemia in patients with primary hypovolemic shock due to acute hemorrhage. A search for endotoxemia in young patients with massive blood loss from severe trauma, carried out immediately and then frequently during the first 48 hours after injury before significant wound infection develops, would help greatly to clarify these issues. To the best of our knowledge, this study has not been done.

The second point Dr. Fine makes is that our experiments do not prove that endotoxemia would not occur in a different kind of experiment than the ones we did. We concur with that view. Briefly, we suppose Dr. Fine would have been more interested in the endotoxin levels of severely shocked animals which had been adequately treated but failed to respond. These experiments would have been difficult to design and conduct because of their length and the problem of definition of adequate treatment and of failure. We submit that the alternative we chose was at least interesting. Positive results would surely have been noteworthy support for Dr. Fine's views. We did sample from the portal circulation in an effort to maximize detection of splanchnic endotoxin in the presence of very low flows, and transfused some of the animals to wash out the splanchnic circulation. Our failure to find either endotoxemia or any anatomic evidence of splanchnic ischemia suggest at least that responses easily elicited in the dog are rare or much less easily elicited in the baboon, or perhaps do not occur at all in this species.

The final group of comments relates to the possible inaccuracy of our Limulus assay technique. Dr. Fine is particularly concerned with occasional positive tests in control periods. Three possible explanations have occurred to us: Haphazard contamination of samples, the presence of very low normally circulating levels which would lead to sporadically positive tests, and finally possible nonspecificity of the Limulus assay test.[1] In each case we would still expect to see more positive tests if additional endotoxin were entering the splanchnic or systemic circulation during hemorrhagic shock. If non-specificity should prove a serious problem, the interpretation of other studies reporting positive results may have to be reconsidered.

There is of course no way we can be absolutely certain our assay technique was flawless. The reader is invited to review the procedures and controls described in our paper. The fact that we found unexpected positive samples and unexpected negative samples does not in itself indict the assay procedure.

We join Dr. Fine in commending Annals of Surgery for permitting this exchange. We also hope other scientists will be stimulated to join us and Dr. Fine in further exploration of what is obviously an incomplete understanding of the relationship between endotoxemia and hemorrhagic shock.

Clifford M. Herman, M.D.
Louis D. Homer, M.D., Ph.D.
Naval Medical Research Institute
Bethesda, Maryland 20014

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September, 1974

Dear Editor:

The past decade has seen increasing concern over electrical safety for hospitalized patients. Safety standards governing how our hospitals and equipment will be built are being written by agencies such as the National Fire Protective Association and Underwriters' Laboratories.

These approaches, however, are largely hardware oriented, and thus either very limited, or expansive in scope. Try to conceive of the difference between applying extreme safety standards to 1) equipment likely to contact the cardiac catheterized patient, or 2) equipment likely to contact an externalized cardiac conductor. The former can include every patient-environment device in an institution; the latter can apply to a select and reasonably well defined set of equipment components.

Why has the hardware approach set the tone for many standards? Because the standards committees are composed largely of technical people unfamiliar with details of clinical practice who see little professional activity toward development of effective safe practices, and who see themselves therefore as protectors of the "Electrically Susceptible Patient." Physician input to, as well as involvement on, standards making committees has indeed been minimal. Participation on committees may be restricted by funding, but input to committees involves only interest and modest investment in time. The fact that accidents occur infrequently cannot continue to lull us into apathy. In order to lay the specter of the "Electrically Susceptible Patient" to rest once and for all I urge professional medical organizations to emphasize to their members the importance of ensuring the following in their own institutions: 1) Protect externalized cardiac conductors from unwanted contacts with the environment. 2) Select thoughtfully the things deliberately connected to externalized cardiac conductors. If the medical profession will concentrate on safe medical management, the technical personnel can concentrate on providing equipment and facilities that are reasonably, and realistically safe.

Karen S. Kagey, M.D.
Peter Bent Brigham Hospital
Boston, Mass. 02115

Book Reviews

Cancer Chemotherapy. Medical Outline Series, Second Edition, January 1973. Edward S. Greenwald, M.D. Henry Kimpton Publishers, London. 464 pages, 4.50 pounds.

The first edition of this book appeared in 1967, consisting of 215 pages with a moderate bibliography. At that time, the author could refer to evidence supporting the fact that in some instances chemotherapy was able to prolong life in childhood leukemia, multiple myeloma and choriocarcinoma. This present volume, six years later, consists of 464 pages with 1,122 references. At this time, the author can state that "only two malignancies, uterine choriocarcinoma and Burkett's lymphoma are frequently cured with chemotherapy, but isolated cases of childhood leukemia, testicular cancer and Hodgkin's disease may also have been cured by this modality." Such represents the rapid development in the field of cancer chemotherapy and well justifies a new edition of this work.

The book begins with a brief chapter on cell kinetics and is followed by a reasonably detailed consideration of the pharmacology of cancer chemotherapy. Individual agents, their usefulness and their hazards are considered. There is a brief but worthwhile chapter on hormone therapy and a valuable consideration of specific problems of toxicity. Particular tumors are then considered along with the treatment of the complications of malignancy. There is a final chapter on the use of chemotherapeutic agents in the treatment of non-neoplastic diseases.

One can commend the author for his careful appraisal of various therapies, the consideration of adequate controls and the particular hazards involved. He is objective and not over enthusiastic. One sees this in his statement "although chemotherapy must still be considered the least important of the three major modes of cancer treatment, which also include surgery and radiotherapy, greater advances have been made in chemotherapy than in the other two areas."

This volume contains information necessary for mature judgment in the care of patients with malignant disease. It also brings the surgeon face to face with the problem of continued care in patients upon whom he has operated for cancer. If, after the surgical extirpation of the malignant lesion, the surgeon wishes to discharge completely to others the responsibility for the subsequent care of his patient, perhaps there is much in this book he need not know. It is becoming apparent, however, as the importance of chemotherapy increases in the care of the patient with cancer, such a decision on the part of the surgeon would be silly, indeed. Either he must become cognizant of the many problems in this field or he must work in close harmony with those who do. Perhaps both are necessary if we are to progress.

The publisher has done a good job. The typing is well spaced and easily readable. With offset printing, good paper and spiral band binding of plastic and cardboard, the price has been kept reasonable.

Nathan A. Womack, M.D.

An ABC of Modern Immunology. E. J. Holborow. Second Edition. 94 pages, 8 illustrations 1968, 1973. Little, Brown and Co., Boston.

This small volume of 10 chapters contains a summary of the principles of immunology (not primarily of tumors), and is presented in an admirable fashion.

The first chapter contains a brief discussion of the "old" features of immunology, starting with the experiences of von Pirquet, coming up to date, mentioning the importance of Medawar's experiments with skin grafts. The author calls attention to the fact that we now know that the complement-fixing antibodies and anaphylactic antibodies, though having apparently identical combining specificity toward a given antigen, are chemically distinguishable from each other as proteins.

Naturally, serious attention is given to immunoglobulins, the group of serum-proteins to which the antibody molecules belong. The five different immunoglobulins (G, M, A, D and E) are described briefly and the structure diagrammed. The author quotes Porter as suggesting a symmetrical structure of four linked peptide chains for the IgG molecule—i.e., two heavy chains and two light chains. Most of the antibody producing cells are found in the spleen, lymph nodes and bone marrow. Of the lymphocyte cells the plasmocyte is best equipped for intensive immunoglobulin production. He calls attention to the fact that the presence of immunoglobulin is demonstrable in many plasma cells by the fluorescent antibody technique of Coombs. Several of the features of pathogenesis and synthesis of immunoglobulins are illustrated by electron micrographs.

In the author's opinion, the total free IgG in a healthy adult is about 80 gm, and is distributed equally between the blood and extravascular fluid, about one fourth passing across the capillary walls each day and an equal amount returning via the thoracic duct. On the other hand he considers the macromolecular IgM to be predominantly intravascular.

Chapter four deals with Cellular Immune Faculties. The author remarks that so far as antibody is concerned "memory" is translated into activity in plasmoblasts, and that "on stimulation these cells behave as primed effectors, committed to a sequence of proliferation and differentiation of clonal character, which results in antibody production that is rapid and profuse, but nevertheless self limited." He calls attention to the fact, now well known, that lymphocytes are very important in the immunologic function of the body. Although they may look alike, functionally they may be quite different.

A separate chapter is devoted to the Immunological Capability of Small Lymphocytes which can initiate immune reactions which are mediated not by circulating antibody, but by direct cellular action. Circulating small lymphocytes play a significant part in initiating primary antibody formation as well. Some lymphocytes have definite properties as mobile antibody-producing cells. We are beginning to visualize the kinds of "recognition at the cellular level that gives the lymphoid tissue its characteristic property of proliferating in response to antigen."

In a chapter on Cell-Mediated Immunity it is brought out that in spite of recent advances we still know less about how cells act as effectors of immune responses than we do about humoral mechanisms. The author goes into detail throughout the book describing the role of allografts in the development of antibodies and the rejection phenomenon. It has been established "that for 'solid tissue' allografts (e.g. skin) antibodies do not usually play an effective part in the rejection process." The importance of lymphocytes in the immunologic process is emphasized. In his discussion of the role of lymphocytes in immunity, the author notes that one of the most important advances in immunology during the past decade is the discovery that "conditioning of progenitors of such antigen-sensitive cells is a function of the thymus. Thymectomy causes a diminution in the numbers of lymphocytes in the blood, lymph and lymphoid tissue, but no significant immunological deficiency.

One chapter deals with intercellular cooperation and lists cooperation between thymus-dependent and bone-marrow-derived cells as an example. Immunological tolerance is, of course, a vital phase of immunity. Important in this consideration is the fact that newborn mice injected with cells from an allogenic donor become tolerant of skin grafts from the same source, thus illustrating that tolerance is as much a specific response to antigen as antibody production. Autoimmunity is discussed in moderate detail.

This small volume contains much valuable information about immunology. Although the title is listed as An ABC of Modern Immunology, it is not designed for the beginner in so far as the definitions and other elementary features are not given. It is clearly written and would be very useful and informative for the physicians and students who have had an elementary course in the subject. The only feature which the reader might criticize is the superfluity of reference to the "skin graft" in illustrating the numerous features of immunology. Obviously, many features of immunology are not covered, but this could not be avoided in such a small volume on the subject.

WARREN H. COLE, M.D.

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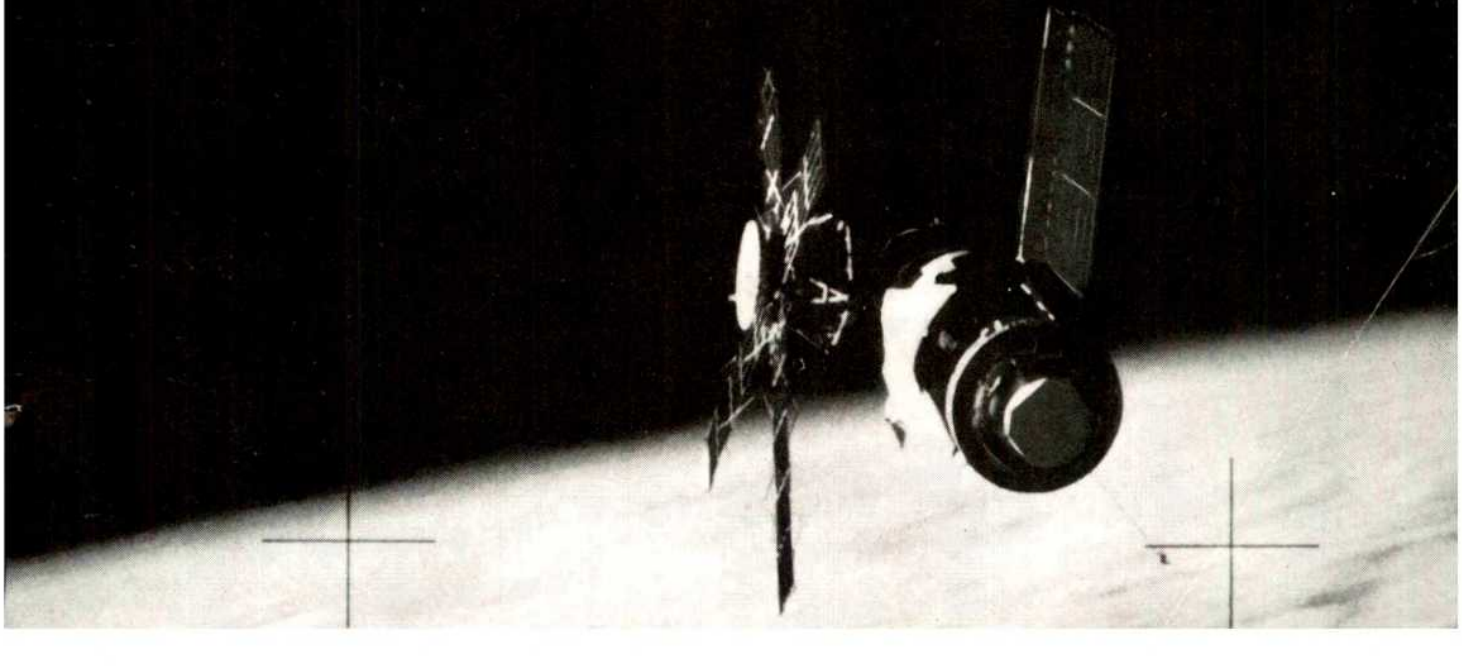

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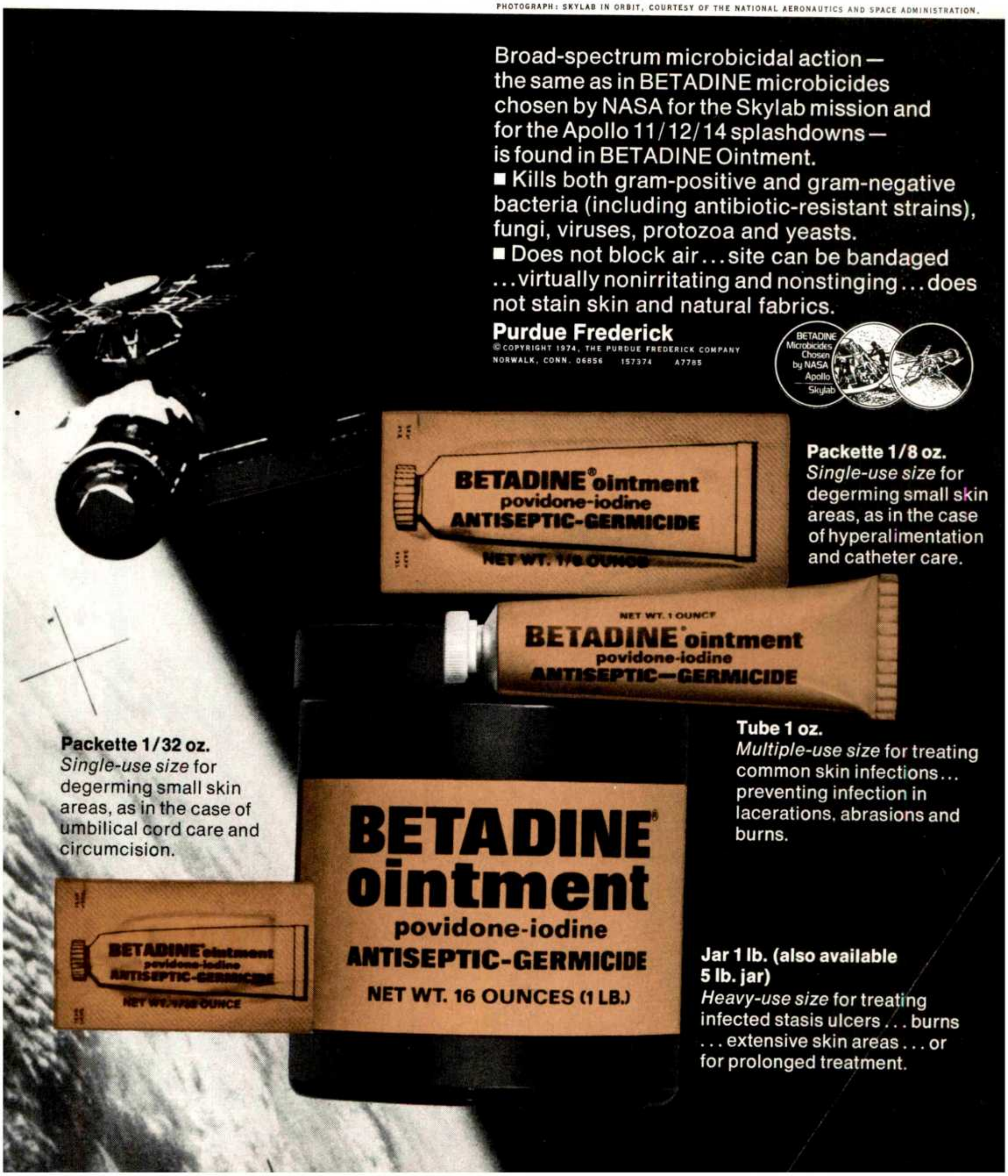

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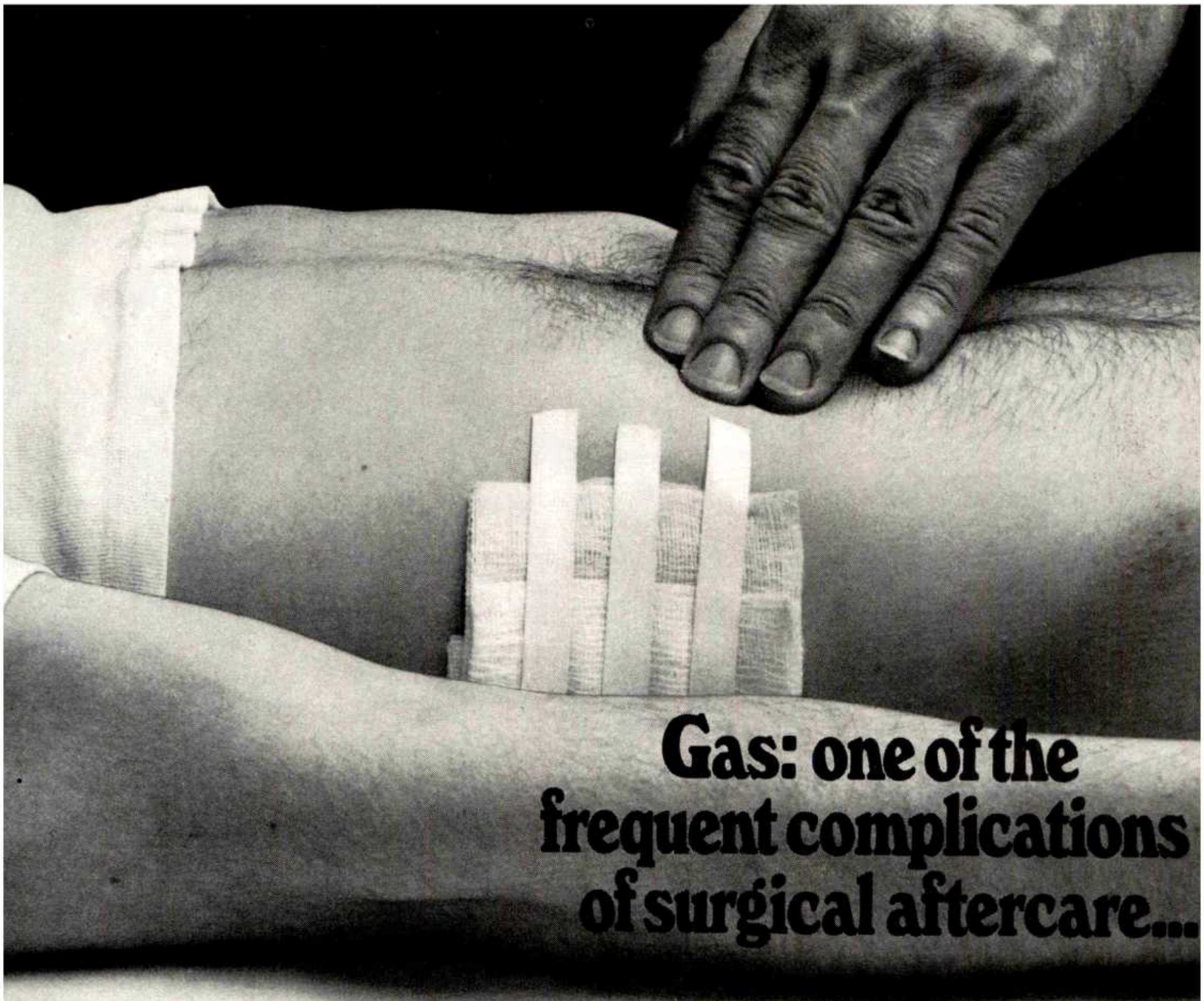

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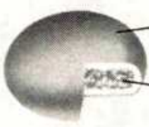

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol. 38*:386, Sept. 1971.
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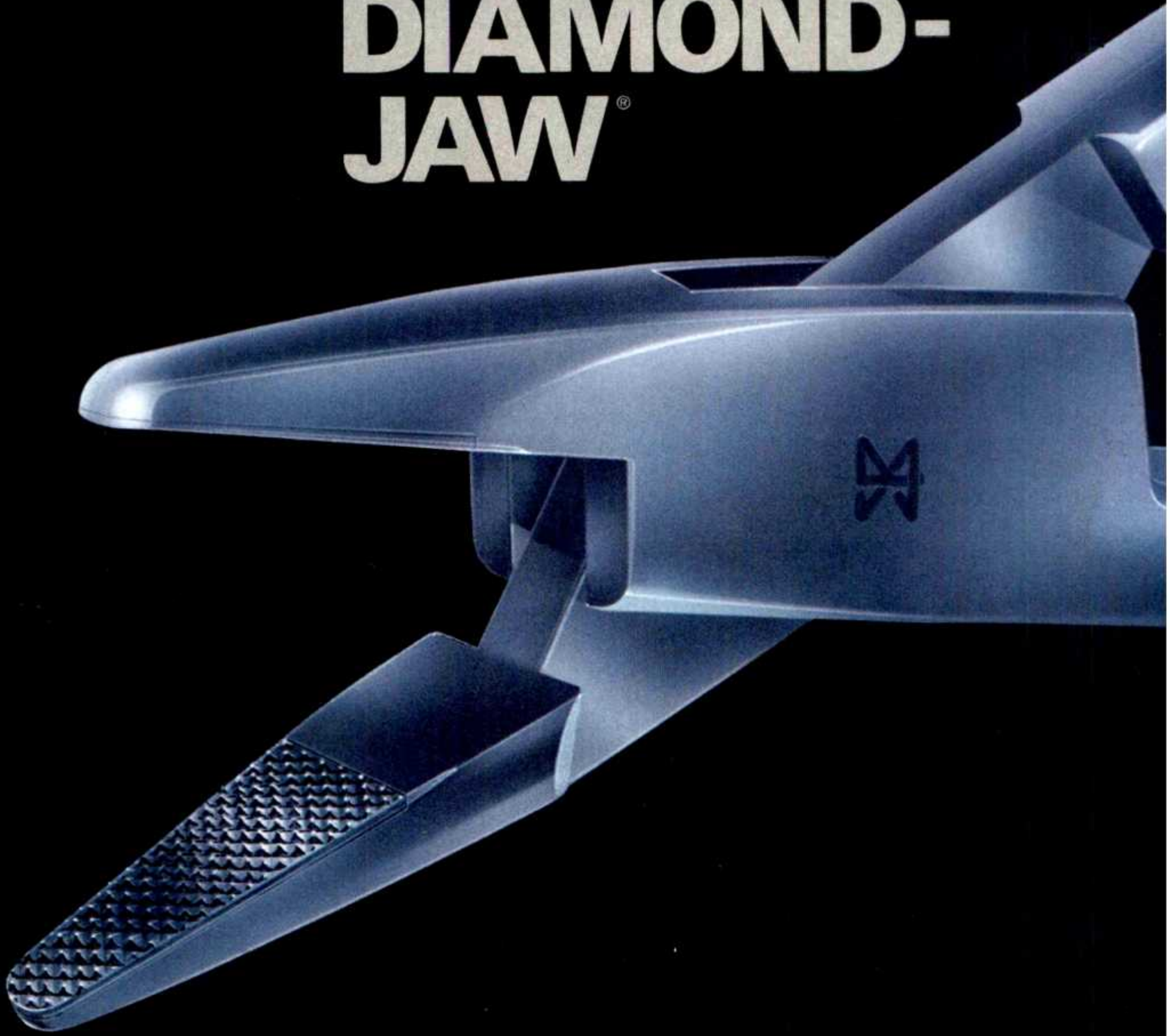

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Malignant Lymphoma: Nodal and Extranodal Diseases. Y. N. Yee, M.D. and J. S. Spratt, Jr., M.D. 412 pp., $17.50. New York, Grune and Stratton, 1974.

LEE AND SPRATT have effectively reviewed a subject that has been confused by changing nomenclature for the past several years. The chapter on "Clinical and Pathological Aspects" is more simplified than past efforts. They discuss Hodgkin's disease as one type of lymphoma and group the other lymphomas in a major separate group of non-Hodgkin's lymphomas. They follow the terminology of Rappaport and therefore the text is easy to follow for anyone familiar with modern oncology.

The chapter on radiotherapy and chemotherapy is quite up to date and includes most of the radiation protocols that have been evaluated for lymphoma. Particularly good is the discussion of chemotherapeutic agents, both singularly and in combination, that have survived good clinical trials with clear documented efficiency.

The chapter on "Major Surgery in Malignant Lymphomas" leaves the reader somewhat confused about the role of extirpative surgery for malignant lymphoma. For the most part, the early chapters have suggested properly that malignant lymphoma is a systemic disease; however, this chapter indicates too great a rule for surgery in the management of lymphoma. The chapter concerned with surgical staging in this disorder is quite good. Lee discusses both the pros and cons of this approach and brings it up to date through 1972 reports. The authors include key investigative clinical series that indicate that approximately one-third of the patients have been incorrectly staged by non-operative means. They emphasize that the major value and benefit of laparotomy including splenectomy, liver biopsy, and abdominal node evaluation should be utilized to determine the extent of the disease and appropriately alter the therapeutic regimen to coincide with the pathological findings.

Perhaps the authors should have included some discussion of the lymphomas realized in the immunosuppressed renal transplant recipients. This would have led to a discussion of tumor immunology as it relates to reticuloendothelial neoplasia.

They do not cover the subject of tumor-specific or tumor-associated antigens documented in lymphomas nor immune responsiveness studied in these patients by authors such as Eibler and Sokal. They also have no discussion pertaining to the role of immunotherapy in these disorders. The illustrations are above average and for the most part are quite helpful in depicting results. The bibliography is quite good. Overall, I think the manuscript is very well done and I am pleased to see that this most interesting disease is summarized for Modern Surgical Monographs.

HILLIARD F. SEIGLER, M.D.

Hodgkin's Disease. David Smithers *et al.*, editors. 258 pages. Churchill Livingstone, 1973.

MANY articles on Hodgkin's disease have appeared in the medical press over the past few years, reflecting updated knowledge on its nature, pathology and treatment. This book, contributed by members of a Lymphoma Unit of the Royal Marsden Hospital, presents a comprehensive review of the subject.

According to the Kaplan-Smithers hypothesis, Hodgkin's disease has its origin in sustained lymphoproliferation, antigenically altered lymphoid cells, and tumor-versus-host reaction. Aspects of epidemiology, clinical presentations, histology, and immunology are presented using case material from their own hospital. The chapters on cytogenetics, cell biology, and experimental immunological studies contained non-clinical and preliminary research findings.

Although Hodgkin's disease is believed unicentric in origin and to spread in a predictable manner by the group at Stanford University, Smithers, *et al.* suggest that the tumor may be either unifocal or multifocal and spread along lymphatics and blood vessels. Specific extranodal sites that can be involved by Hodgkin's disease are discussed in separate chapters (lung, bone, skin, nervous system, bone marrow and post-mortem studies). Their experiences with the various methods used to study the extent of disease such as lymphography, isotope scanning, laparotomy and splenectomy are given. Survival data, their current radiotherapy treatment policy and chemotherapeutic programs are presented and discussed. In general, their approach is similar to that practiced in this country except for minor modifications. This book certainly fulfills its purpose in presenting a general overview of Hodgkin's disease for those working on isolated parts of the problem as well as for the physician and surgeon who are only occasionally involved in its treatment.

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Fundamentals of Colon Surgery. Leslie W. Ottinger, M.D. 238 pages. Boston, Little, Brown and Company, 1974.

THIS MONOGRAPH, after a page for Preface and one for acknowledgments, is comprised of 10 chapters distributed through 238 pages and concludes with an index of 35 pages. There is a modest reference list at the end of each chapter.

The first chapter, "General Considerations," is followed in numerical sequence by the following chapter headings: "Surgical Emergencies;" "Acute Inflammation;" "Ulcerative Colitis;" "Granulomatous Diseases of the Colon;" "Ischemic Lesions of the Colon;" "Problems of Colon Fixation;" "Benign Tumors;" "Malignant Tumors of the Colon, Rectum and Anus;" and lastly, "Problems of the Lower Rectum and Anus."

There are 16 pen and ink drawings which are simplistic in their diagrammatic representation. In one (Fig. 1-3), the disposition of the greater omentum in relation to the transverse colon and pancreas is anatomically incorrect.

Initially, in the text, the author refers incorrectly to diverticuli, later and correctly to diverticula, then to diverticulae, and finally back to diverticuli. The word *very* is used too frequently to attain its desired effect for emphasis. Also, to use such phrases as: "right upper abdomen" (page 14); "Suggested by radiology" (page 21); "pathological examinations" (pages 111, 208), and "work-up of a fever of unknown origin" (page 44) certainly does not equate with critical writing.

Sentence constructions are too frequently confusing as exemplified by the following: "Initially, management of obstructing lesions must encompass those principles essential to the successful management of colon obstruction, whatever the etiology." (page 190). Also, the error in the statement ". . . . and the circular muscle layer is thrown into transverse folds." (page 59). It is the mucosal and not the circular muscle layer that is "thrown into transverse folds."

Despite the title of the text, an inordinate amount of space is given to a discussion of appendicitis. The listing of the references does not follow the universally accepted format in that the titles of the publications are listed first rather than an alphabetic list of the names of the authors. This is an annoying inconvenience to the reader. Reilly is incorrectly referred to as Rellig, both in the text and reference list respectively (pages 73 and 74). The references are poorly selected since many of the classic articles pertaining to the various subjects discussed have been omitted. It is of interest to observe that not one reference is given to the subject of intussusception. Instead the author refers the reader to the pediatric literature on this subject.

In general, the text is loosely written, extremely wordy, poorly punctuated, has frequent misspellings, and is boringly repetitious. There is lack of clarity and brevity of exposition, and the poor continuity in thought expressed precludes a logical sequence in arrangement of the paragraphs. Furthermore, it is difficult to escape the impression that the book was assembled in a hurry both by the author and the publisher.

On completion of the review of this monograph the pertinent question is: "Who is it written for?" In his Preface the author states: "Its main purpose is to serve the surgical resident, . . . and as a handbook for those responsible for the education of surgeons." If so, I fear it has missed its mark.

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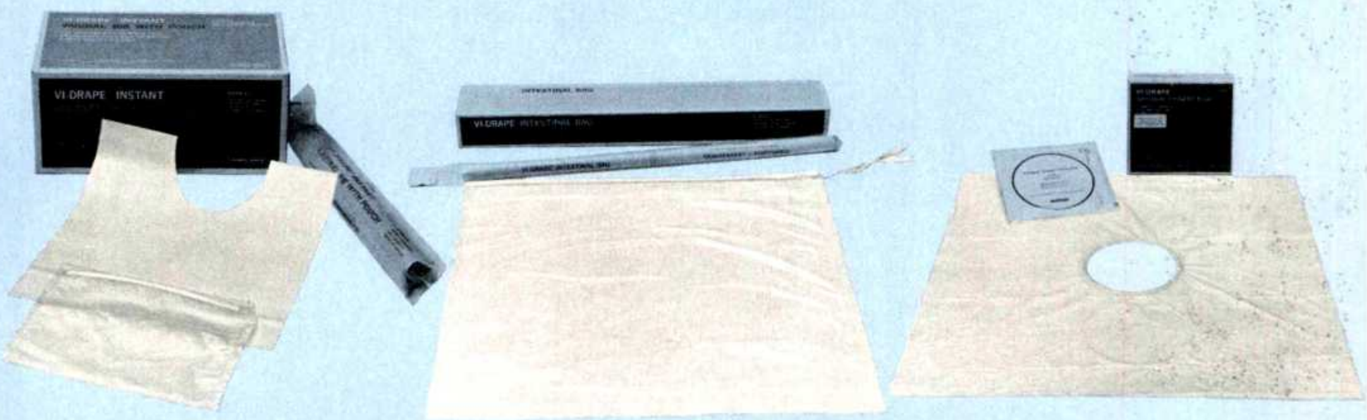

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Occult Breast Carcinomas Detected By Xeroradiography:

Clinical Considerations

LAWRENCE J. MALONE, M.D.,[*] GLORIA FRANKL, M.D.,[†]
RICHARD A. DORAZIO, M.D.,[*] JOHN H. WINKLEY, M.D.[*]

One hundred and eighty-five breast cancers were demonstrated by xeroradiography in 6,238 patients. Sixty-two cancers were occult, and constituted one-third of the demonstrable breast cancers. Some of the patients with clinically nonpalpable carcinomas had high risk factors known to be associated with the development of breast cancer. The diagnosis was usually established and confirmed by wide excisional biopsy of the area containing the suspicious lesion. In some instances the lesion was localized preoperatively by xeroradiography using a technique of skin markings. Specimen xeroradiography was utilized if there were calcifications seen on the preoperative xeroradiograph. There was a significantly decreased incidence of axillary node metastases in the occult cases when compared to the dominant mass cases.

*From the Departments of Surgery and Diagnostic Radiology,
Southern California Permanente Medical Group and
Kaiser Foundation Hospital,
Los Angeles, California*

EARLY DIAGNOSIS of breast cancer remains an elusive goal. Xeroradiography can detect many small cancers before they are noted by the patient or her physician. The term *xeroradiography* is derived from the Greek *xero-* meaning dry, *radio-* alluding to the role of radiation or x-ray, and *graph-* denoting record. Xeroradiography is a relatively new imaging process, especially valuable in the field of mammography, where it is uniquely applicable because of its effectiveness in the low KV range. Xeroradiography is a process of development, substituting a selenium-coated plate for x-ray film.

The advantages of xeroradiography are: 1) xeroradiography is a rapid and dry process; the completed image is delivered from the machine in 90 seconds; 2) in the low KV range, as used in breast diagnosis, there is a significant (about 35%) reduction in radiation exposure; 3) the examination is no more (or even slightly less) expensive than x-ray mannography; 4) all of the breast-skin, ducts, vessels and deep structures, are well seen; 5) increased resolution, permitting identification of smaller structure, especially tumor calcifications which are so important in the early detection of breast carcinoma; 6) xeroradiographs are more easily interpreted, without special means of viewing.

There are two relative disadvantages of xeroradiograph: 1) the equipment is not as yet available in all areas; 2) the radiologist must undergo a relearning process in the evaluation of these images, with special emphasis on duct patterns which are so very important in breast cancer detection.

The views obtained depend on physical findings, but if physical examination is unremarkable, and if there are no remarkable findings on the xeroradiographs studied by the technologist, then two views of the breast are obtained; mediolateral and carniocaudal images.

Xeroradiography complements physical examination of the breast, and does not replace a careful evaluation of the patient by her physician. Nonetheless, it can detect occult carcinomas in the breast in the absence of physical findings, and it can direct the surgeon to suspicious areas in nodular breasts. Dominant breast masses continue to require biopsy. Sixty-two occult carcinomas of the breast were detected during the first 21 months of operation of the Xeroradiography Unit at this Center, and they constitute the basis of this report. An occult carcinoma of the breast is defined as a cancer unassociated with a palpable mass, a cancer detected by xeroradiography alone.

Materials and Methods

Between October 15, 1971 and August 15, 1973, 6,238 patients underwent breast xeroradiography at the Kaiser Permanente Medical Center in Los Angeles, and 185 breast

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Submitted for publication May 30, 1974.

[*] Department of Surgery.

[†] Department of Diagnostic Radiology.

Reprint requests: Dr. Gloria Frankl, 1505 North Edgemont, Los Angeles, California 90027.

TABLE 1. *6,238 Patients Examined by Breast Xeroradiography in 21 Months*

	No. of Cases	% of Cases
Total Biopsies	788	12
Benign Biopsies	603	9
Malignant Biopsies	185	3
Occult Cases (Non-palpable)	62	1
Dominant Mass (Palpable)	123	2

cancers were detected. A total of 788 biopsies were done in these 6,238 patients. One hundred twenty-three of the breast cancer patients had a dominant mass on physical examination. The other 62 cancers were occult and not associated with a palpable mass. The inpatient and outpatient records, the xeroradiographs, and the pathological reports were all reviewed. It was possible to ascertain that these 62 occult cancers were clinically undetectable. Table 1 summarizes our experience.

Results

Sixty-two occult carcinomas were discovered in 61 women. One patient had bilateral, nonpalpable carcinomas with 58 negative bilateral axillary nodes at surgery. The indications for xeroradiographic study in these women with occult breast cancer were fibrocystic disease, previous mastectomy for cancer, previous biopsy for benign disease, nipple discharge, inverted nipples, and unknown site for primary cancer. Of note is the finding that 12 women had a family history of breast cancer involving a mother, sister, or maternal aunt. Family history was not listed as the major cause for referral in any case, but it was noted on the radiologist's mammography history sheet, and it may have influenced the patient's physician to order the xeroradiographic examination.

Of the 61 women with occult carcinomas, 45 were postmenopausal and 16 were premenopausal. Nineteen women were nulliparous. The importance of late parity as a high risk factor in the development of breast cancer is not generally appreciated. Our definition of late parity means that the woman had her first child at the age of 28 years or later, and 15 of our 62 occult cancer patients were in this category of late parity. Previous breast biopsy for benign disease in the same breast had been performed in 15 of 61 patients. Women in these high risk groups are analyzed in Table 2.

Fifty-five carcinomas were treated by radical or modified radical mastectomy. Simple mastectomy or biopsy alone was performed for the other six cases. In 18 of the 55 occult cancers treated by radical or modified radical mastectomy, there were associated axillary node metastases. Two patients had metastases to bone or lung at the time of diagnosis of occult breast carcinoma, and the axillary nodes were not sampled. Thus, there were 20 occult cancer patients (32%) who had evidence of metastatic disease. For comparison, 62 (51%) of the women with a dominant mass and a positive xeroradiograph had metastatic disease (Table 3).

TABLE 2. *62 Occult Breast Cancers—High Risk Factors*

	No. Patients	% Patients
1. Previous Mastectomy	9	15
2. Nulliparous	19	31
3. Late Parity (Age 28 or later)	15	24
4. Family History of Breast Cancer	12	20
5. Prior Benign Biopsy, Same Breast	15	24

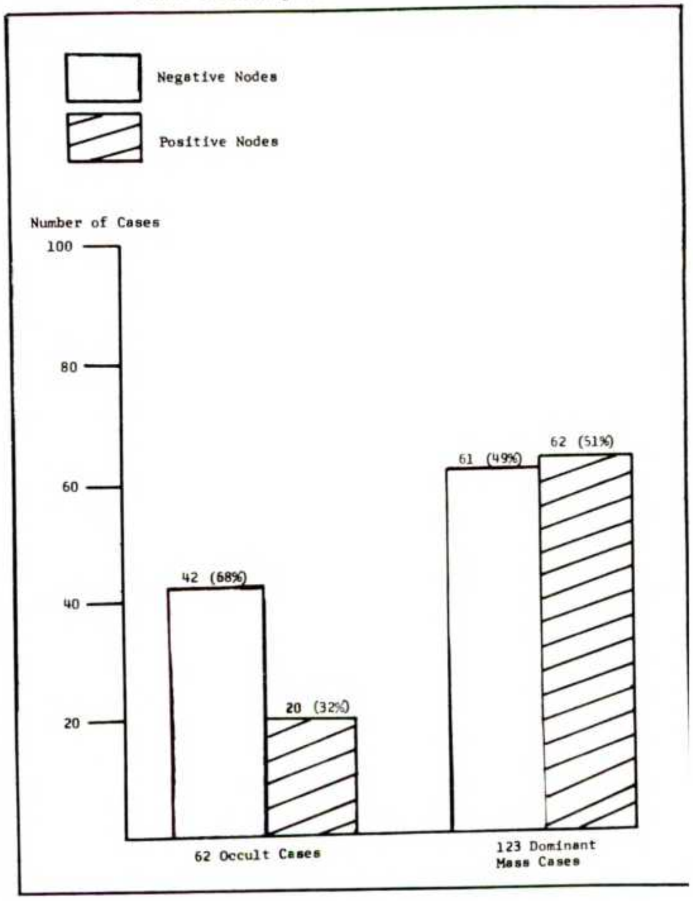
Unfortunately, accurate measurement of the size of the cancer was not available in many cases, and estimates were noted in others. Seven cancers were specifically measured to be less than one centimeter, and no axillary node metastases were noted in these cases. Twelve cancers were noted to be one centimeter, and three of these were associated with positive axillary nodes. The small numbers and the lack of exact measurements in many cases make further meaningful analysis impossible.

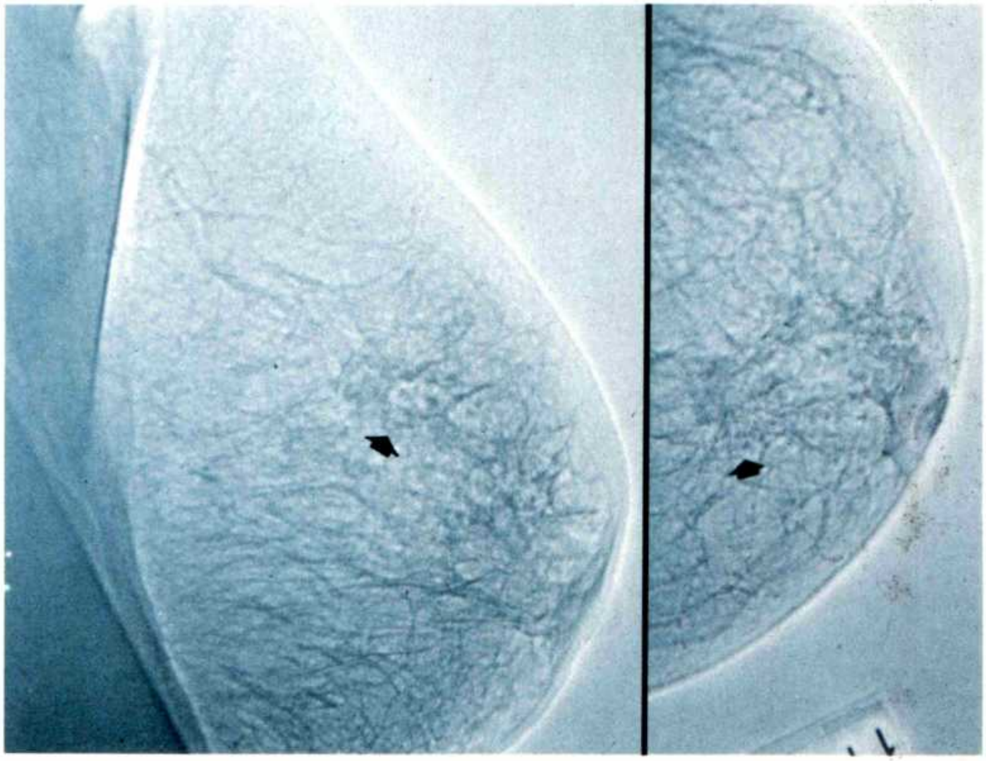
The pathological findings in the 62 occult breast carcinomas are listed in Table 4. Infiltrating ductal carcinoma was the diagnosis in 59 cases. Only one lobular carcinoma was noted in this series.

Xeroradiography Findings and Extent of Disease

The xeroradiographic findings in breast cancer include

TABLE 3. *Axillary nodes in 185 breast cancers.*





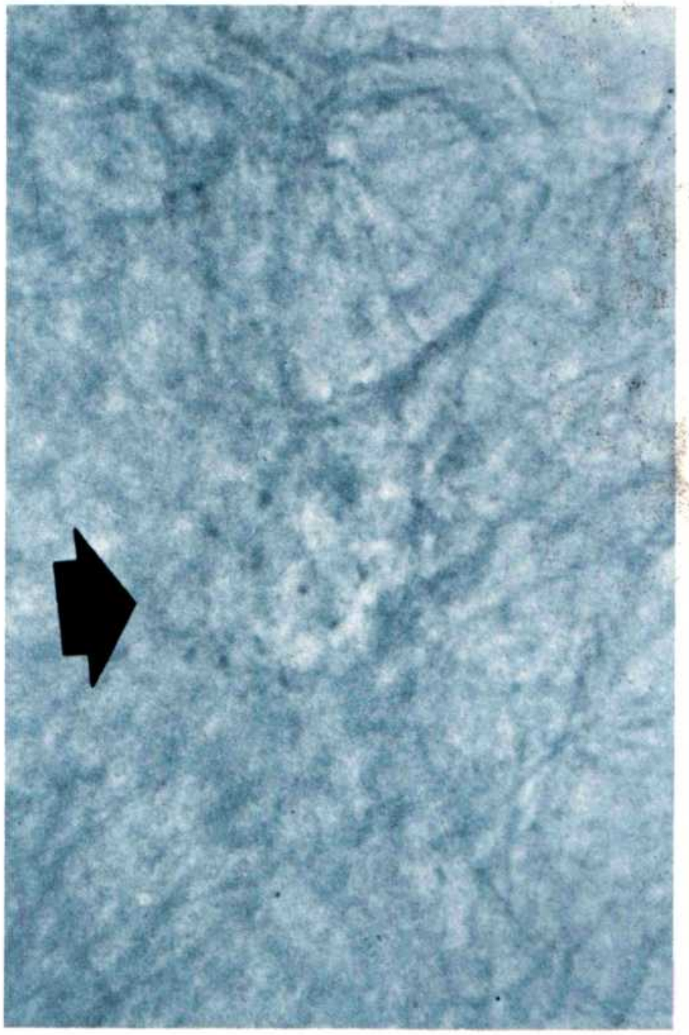


FIG. 1. Occult Breast Carcinoma detected by xeroradiography: Clinical Considerations. 61-year-old woman with discharge right nipple. No associated palpatory findings. Xeroradiograph shows spiculated mass with irregular and ill defined borders. Mass is incorporated in prominent ducts, and there are innumerable minute calcifications contained within the mass. Diagnosis-carcinoma; pathology-infiltrating ductal carcinoma with negative axillary nodes. (Left to right) A. Right lateral xeroradiograph. B. Caudal xeroradiograph of right breast. C. (bottom) Close-up view of calcifications.

mass-density, malignant tumor calcifications, altered duct pattern, increased vascularity, skin changes and nipple retraction. All cases in this series were reported as to the presence or absence of malignant calcifications. The other findings were present in a variable number. Table 5 correlates the xeroradiographic findings of mass only, malignant calcifications alone, or the combination of both mass and calcifications with the presence or absence of axillary node metastases. The finding of malignant calcifications by xeroradiography was more often associated with metastases than a finding of mass alone. Over half of the patients with both mass and malignant calcifications had metastases. Some of the xeroradiographic findings in malignancy are demonstrated in Fig. 1.

Surgical Management of Patients With Occult Breast Cancers

In all cases of carcinoma diagnosed by xeroradiography at this institution, the referring physician was notified directly by the radiologist of this finding. The occult cancer patients were scheduled for early biopsy and possible mastectomy. Diagnosis was usually established by wide excisional biopsy of the area containing the suspicious lesion. If there were calcifications seen on the preoperative xeroradiograph, an examination of the surgical specimen was done, and the site of disease was marked by the insertion of a radiopaque needle into the lesion. Thus, excision of the correct area was also confirmed at the same time. Samples for frozen section examination were then taken from the marked area. The specimen correlation added approximately 10–15 minutes to the operating time. If the frozen section were positive,

TABLE 4. *Pathology of 62 Occult Breast Carcinomas*

Infiltrating Ductal Carcinoma		59
Includes Comedocarcinoma	3	
Papillary	1	
Paget's Disease	3	
Noninfiltrating Ductal Carcinoma		1
Mucoid Carcinoma		1
Infiltrating Lobular Carcinoma		1

mastectomy immediately followed the report from the pathologist.

In six cases of occult breast carcinoma, final diagnosis could not be made by the pathologist until the permanent histological slides were made and until appropriate multiple samples of the marked area were studied.

Sometimes, in difficult cases, the lesion was localized preoperatively in the Xeroradiography Suite by a technique devised by one of the authors (G. F.). Strips of tiny plastic numbers are applied to the patient's breast, vertically and horizontally, to enclose the quadrant containing the occult carcinoma. Using a mapping technique, a wetted silver nitrate applicator stick is used to mark the skin overlying the lesion in two projections. The silver nitrate is readily detectable xeroradiographically, the colored mark on the skin will resist surgical prep, and the solution does not burn or hurt the patient. The surgeon then has a guide to the site of a nonpalpable, suspicious lesion. He performs his biopsy between the two silver nitrate marks on the skin.

Discussion

Xeroradiography replaced conventional mammography as the method of x-ray diagnosis of breast disease at the Los Angeles Kaiser Foundation Hospital-Sunset Facility in October, 1971. The technical superiority of this procedure has been well demonstrated by the work of Wolfe[5] and Martin,[4] and has been corroborated by the report of Frankl and Rosenfeld[2] from this institution.

One hundred and eighty-five occult breast carcinomas were demonstrated by xeroradiography in 6,238 women. *Sixty-two (34%) of the detected breast cancers were occult, nonpalpable lesions*. The women who were referred for breast xeroradiography, and in whom breast cancers were found, represent a somewhat selected group. A general screening program was not in effect. A significant number of occult cancer patients had a previous contralateral mastectomy, a prior biopsy, or a family history of breast cancer. Late parity has been noted by Mac Mahon *et al.*[3] as of possible significance in the development of breast cancer, and our series of occult breast cancer patients corroborates the importance of this high risk factor. Nineteen women were nulliparous. Certainly, xeroradiographic study, as well as routine physical examination, is indicated for all women who fall in the high risk categories which are noted above and which are listed in Table 2. Ultimately, it is hoped and expected that all women over the age of 35 in our medical plan will be screened by xeroradiography. It is of interest that we have never demonstrated an occult breast cancer in a woman under the age of 35 years.

TABLE 5. *Xeroradiographic Findings and Extent of Disease in 62 Occult Breast Carcinomas*

Xeroradiographic Findings	Total Cases	Positive Axillary Nodes and/or Distant Metastases		Indeterminate Cases*
Mass Only	21	3/21	(14%)	0
Malignant Calcifications Only	16	4/12	(33%)	4
Mass and Malignant Calcifications	25	13/24	(54%)	1

* In 5 cases without evidence of metastases only biopsy or simple mastectomy was done.

Of the 185 carcinomas demonstrated by xeroradiography in this study, 123 were associated with a dominant mass on palpation. Sixty-two (51%) of these dominant mass cases had positive axillary lymph nodes. Of the occult carcinomas, 20 of 62 (32%) had evidence of spread to axillary nodes or of distant metastases. Fisher *et al.*[1] note that 20% of breast cancers less than one centimeter in size will be associated with axillary node metastases. His study generally shows that larger cancers are associated with greater axillary node involvement, increased rate of recurrence, and a higher mortality. Our study tends to confirm the importance of finding tiny cancers.

Will xeroradiographic detection of early breast cancer improve survival in such patients? Future studies will no doubt elucidate this matter. Decreased axillary node involvement in occult breast cancer provides some encouragement that the ability to diagnose breast cancer before it is clinically detectable may be the key.

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Significance of a Solitary Lung Shadow in Patients With Breast Cancer

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From 1949 through 1972 at Memorial Sloan-Kettering Cancer Institute, 72 breast cancer patients developed a synchronous or metachronous solitary lung shadow. Forty-three had separate primary lung cancers; 23 had breast carcinoma metastases and six had benign lung lesions. Of these, 47% were asymptomatic and the lesions were discovered by routine chest roentgenograms. Among 49 patients who underwent pulmonary procedures, secondary involvement of regional lymphatics was noted in 22, nine of which were daughter metastases secondary to the breast deposit. In such a setting, a radical lobectomy (or pneumonectomy) would seem the operation of choice. Four patients who had primary lung cancer and five patients with pulmonary breast metastases survived five years after the thoracic procedure. Prolonged survival in these patients bore no relationship to age, sex, state of axillary lymph nodes or length of interlude between the breast and the lung cancer. Early diagnosis, the extent of the cancer and adequate excision seem to influence end results. When other primary cancers were present, in addition to those of breast and lung, these did not seem to diminish the chance for survival provided they were treated as if they existed alone. The need for strict periodic and continual followup examinations, not only in breast, but also for all cancer patients is essential for early detection of metastases or new primaries. Chest roentgenograms are an integral part of such a plan. The ambiguity of a solitary lung shadow (or at the most two or three opacities) with a known primary breast cancer requires clarification without delay as to its histologic nature so that proper treatment can be instituted and an accurate prognosis given.

A SINGLE LUNG SHADOW, either synchronous or metachronous, with an extra-thoracic cancer is a diagnostic and therapeutic dilemma.[1,2,6-11]

Until recently, when such an opacity was discovered, it was assumed to be a metastasis and a visible representative of others more cryptically placed elsewhere. It was also believed to be the harbinger of many more deposits that would inevitably appear and as a result of such pessimism, no action was taken or only palliative efforts were made.

As thoracic surgery matured and these conservative approaches proved unrewarding, attempts were made to excise these lesions.[8-11] As a result, it became evident that the shadow was not always a metastasis as originally assumed, but proved instead to be a new primary lung cancer or occasionally a benign process. In addition, even if it were malignant, palliative benefits and long-term survival resulted which might not have occurred had it been allowed to remain untreated.

Clinical Material and Methods

This report describes the experience at Memorial Sloan-Kettering Cancer Center with patients who had breast carcinoma in whom a solitary lung shadow appeared.

During a 23-year period, 1949–1972, 72 patients presented with the above clinical setting: 43 had separate primary lung cancers; 23 had breast cancer metastases and six had benign lung lesions.

Of the 66 cancer patients, 53 could be evaluated for five years or more, a period traditionally used as an arbitrary measurement of cancer control. All patients but one had complete followup.

The cytologic and histologic studies of both the breast and the lung lesions have been reviewed.

Sex and Age Incidence

In the lung cancer group, there were 39 females and 4 males. In the metastatic (23) and benign groups (6), all were females. In primary breast cancer the ratio of females to males is 100 : 1.[12] However, in this group where primary cancers of the breast and lung occurred in the same patient, the ratio was 10 : 1.

The ages at the time the lung lesions were detected ranged 38–77 years with an average of 59 years. The peak

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age incidence was similar in all three categories (primary, metastatic and benign) occurring between the fifth and seventh decades.

The average age when breast cancer was diagnosed was 52 years; for primary lung 51 years; for metastatic breast 48 years and 50 years for benign lesions.

Signs and Symptoms

Fifty-three per cent (35/66) of the patients with malignant lung lesions had symptoms, some of which were multiple. These included cough, hoarseness, chest pain, dyspnea, hemoptysis, fever and superior vena caval syndrome. These were more frequent in the primary than in the metastatic group but were non-specific for either condition.

Forty-seven per cent (31/66) were asymptomatic: 12 with primary lung cancer and 19 with breast cancer metastases. Of the primary lung cancer group, three patients had their lung lesions discovered by routine roentgenography during followup examinations or as a preparatory workup for breast cancer treatment.

Of particular interest are nine patients whose lesions, upon autopsy, proved to be lung cancers rather than metastases.

All six patients with benign lung lesions were asymptomatic.

A history of heavy cigarette smoking (minimum 1 pack/day/20 years) creates a bias in favor of the lung shadow being of pulmonary origin. Of those whose tobacco habits were adequately documented: 17 of 27 in the lung cancer group were heavy smokers; one of 12 in the metastatic group and one of five in the benign group.

Interval From Breast Primary to Lung Lesions (Table 1)

Eighty-six per cent (62/72) of the shadows were metachronous and appeared from three months to 23 years after treatment of their primary breast carcinoma. Seventy per cent of these appeared five years or more after treatment of the breast primary. In 33% (9/27) the lung lesions appeared after ten years. Ten patients had synchronous primary breast cancers and lung lesions: eight had primary lung cancer; one had a breast metastasis and one had a benign lung lesion.

TABLE 1. *Interval from breast carcinoma to appearance of lung lesion.*

Years	TOTAL	Primary	Metastatic	Benign
Synchronous	10	8	1	1
< 2	6	5	1	--
2 - 5	30	15	12	3
6 - 10	18	10	8	--
> 10	9	6	1	2
% > 5 years	70% (27/39)	69% (16/23)	81% (9/11)	40% (2/5)
% > 10 years	33% (9/27)	33% (6/18)	20% (1/5)	50% (2/4)

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TABLE 2. *Radiographic diagnosis.*

Radiographic diagnoses	TOTAL	Histologic diagnoses	
		Primary	Metastatic
"Primary"	11	10	1
"Metastatic"	14	8	6
"Primary vs. Metastatic"	25	14	11
Others (granuloma benign etc.)	16	11	5
% Correct Diagnosis	24% (16/66)	23% (10/43)	26% (6/23)

All patients with benign lung lesion were asymptomatic.

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Radiographic Findings (Table 2)

In analyzing the opacity, the radiologist was often tempted to give histologic designations only 24% of which were correct.

In five patients, instead of a single lesion demonstrated on x-ray (by all techniques) two to three were found at exploratory thoracotomy and they were usually confined to one lobe. In three patients these proved to be individual separate primary lung cancers; two others had multiple breast cancer metastases.

Bronchoscopy and Cytology

Fifty-four patients were bronchoscoped (29 with primary lung cancer, 21 with breast metastases and four with benign lesions). Six had positive biopsies: five with primary lung cancer and one with a breast metastasis. Biopsies were not done in 18 patients because: a) the lesion was peripheral and was considered too small (less than 2 cm) to yield significant data; b) presumed dissemination of cancer did not seem to justify it; and c) the patient's general condition was too poor.

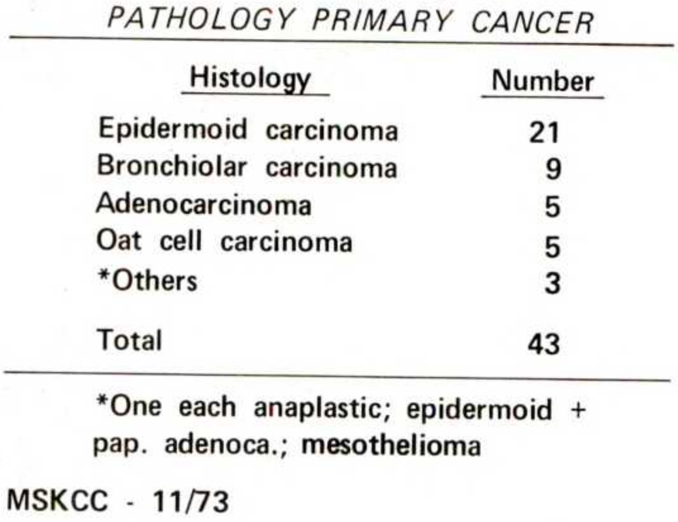
Cytologic studies were done in 59 patients. Cancer cells were found in 59% (19/32) of the primary lung cancer group and 5% (1/21) of the metastatic group. All six benign lesions had negative cytologic studies.

Pathology of the Primary Malignant and Benign Lung Lesions

Of the primary lung cancers (Table 3), there were 21 epidermoid, nine bronchiolar and five oat cell carcinomas. There were three additional variants of lung cancer: mixed adeno-squamous, anaplastic carcinoma and a mesothelioma. Five adenocarcinomas resembled breast cancer but were believed of lung origin although it is often difficult for the pathologist to distinguish between these ambiguous conditions. The criteria used in an attempt to resolve this dilemma are discussed later.

Of the patients with benign lung lesions (Table 4), two

TABLE 3. *Pathology primary cancer.*



PATHOLOGY PRIMARY CANCER

Histology	Number
Epidermoid carcinoma	21
Bronchiolar carcinoma	9
Adenocarcinoma	5
Oat cell carcinoma	5
*Others	3
Total	43

*One each anaplastic; epidermoid + pap. adenoca.; mesothelioma

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had hamartomas and one each had a neurilemmoma, a granuloma, a dermoid cyst and a benign fat pad.

Pathology of the Breast Cancers

Forty-three patients had infiltrating duct cancer: 24 in the primary lung group and 19 in the metastatic group. Five others had lobular carcinomas, two had colloid, two had medullary cancers and one had papillary cancer. All these last named histologic types occurred in patients with primary lung cancer.

In 13 patients, the generic term adenocarcinoma was used without adjectival specification: nine in the primary and four in the metastatic group. One half of the patients in this series had metastases in the axillary lymph nodes.

Pulmonary Lymph Node Involvement

The regional pulmonary lymphatics were examined either in the resected specimen or, if resection was not possible, a representative extrapulmonic lymph node was excised for study.

In the primary lung cancer patients, 50% (13/26) of the pulmonary lymphatics were involved: ten in both hilar and mediastinal locations; two confined to the hilum and one in the mediastinum alone.

In the metastatic group, 39% (9/23) of the pulmonary lymphatics contained daughter or second generation deposits: seven in both hilar and mediastinal locations and two confined to the hilum alone.

It is probable that even more nodal metastases were present because at first, no effort was made to remove these for biopsy, for when a lesion was found the surgeon would sometimes be content to biopsy the lung tumor alone. In addition, in resected specimens the state of mediastinal lymphatics could be determined only if these were included as part of a radical lobectomy or pneumonectomy which was not universally performed.

Multiple Primary Cancers (Table 5)

Of those patients with a primary lung cancer, six had a third cancer and two had four separate carcinomas (one of whom also had a hamartoma of the lung).

Three patients in the metastatic group had another primary cancer: one each of colon, cervix and the opposite breast.

Treatment

Seven of the 43 patients with a new primary lung cancer had no active treatment for it. Six of these were assumed to be uncontrollable breast cancers until autopsies revealed the correct diagnoses. The seventh patient's cancer was too advanced when first seen. Of the remaining 36 patients, 18 had surgery and the other half had either radiation and/or chemotherapy.

All patients in the metastatic and benign groups had some form of pulmonary excision.

There was no postoperative morbidity and only one death from hemorrhage following exploratory thoracotomy and biopsy for an epidermoid carcinoma of the lung.

When excision was considered inadequate, irradiation and chemotherapy were used alone or in combination.

Results

Survival is measured from the treatment of the pulmonary cancer.

TABLE 4. *Benign Lung Lesion Associated with Breast Cancer* (1949–1972).*

Patient	Interval breast and lung lesion	Breast therapy	Associated lung lesion	Remarks
M.S. 52 F	Synchronous	Radical mastectomy	Neurilemmoma	Coin lesion on x-ray – asymptomatic
M.S. 61 F	4 months	Modified radical + p.o. R.T.	Hamartoma	
M.K. 57 F	2 years	Radical mastectomy	Granuloma vs. staph abscess	Coin lesion on x-ray – asymptomatic
E.L. 43 F	5 years	Radical mastectomy	Dermoid cyst	Metastatic disease to bone and ovaries
M.B. 52 F	13 years	Bilateral radical mastectomy	Hamartoma	Admitted for an aspirated foreign body
I.G. 63 F	13 years	Radical mastectomy	Benign fat pad	Minimal chest wall recurrence present

* One additional patient had synchronous primary lung cancer and hamartoma in same lung.

TABLE 5. *Multiple Primary Cancers.*

Primary breast and lung ca	Primary colon ca	Second breast ca	Others
1	+		
2	+		
3	+		
4	+		
5			Epidermoid ca - esophagus
6			Teratoma testis
7		+	Lymphosarcoma rectum
8			Thyroid ca, basal cell ca.

Three patients in metastatic group had double primary cancers : one each had adenocarcinoma of colon, epidermoid carcinoma of cervix, adenocarcinoma (second) breast.

Primary Lung Cancer

Thirty-seven of 43 patients with primary lung cancers qualified for five-year survival analysis: 30 received treatment of varying forms and seven had none.

Twelve of the 30 patients had pulmonary excisions; four survived five years or more of which three were asymptomatic, their lesions having been discovered by routine follow-up chest x-rays after treatment of the breast cancer, eight months, nine months and eight years later. Two of the four survivors had a third primary cancer and one also had a hamartoma. One patient died of breast cancer four years, four months after excision. Another was lost to followup after three years and four months having shown no evidence of either cancer.

Of the five-year survivors, three had infiltrating duct and one had colloid carcinoma. The axillary lymph nodes contained metastases in two specimens; one had negative lymph nodes and in one the state of the nodes was not recorded.

The pulmonary lesions in 18 patients were either inoperable or unresectable and radiation and/or chemotherapy were used.

Six patients had various types of pulmonary excisions less than five years ago. Five of these are without evidence of either lung or breast cancer (10, 38, 39, 40 and 58 months later respectively); one patient is living with chest wall recurrence from breast cancer 36 months after pulmonary resection. Thirty-eight patients in this group died: 32 from lung cancer; two from a breast cancer; four from other causes (two with cancer present).

Metastases From Breast

Sixteen of 23 patients had breast metastases excised more than five years ago. There were five survivors all of whom were free of recurrence (Table 6). Of these five year survivors, all had infiltrating duct carcinoma two of whom initially had axillary lymph node metastases; in two, these nodes were negative and in one, their state was not recorded.

Five patients died of disseminated breast cancer two years or more after their pulmonary procedure. Six other patients survived less than two years following lung excision.

Seven patients had various types of pulmonary excisions less than five years ago. Two are without evidence of lung or breast cancer (at 30 and 37 months); four died of disseminated breast cancer, three of whom lived beyond two years. One additional patient died of tracheo-esophageal fistula 32 months after lung therapy.

Discussion

Usually when an extrathoracic cancer metastasizes to lung, it is manifested from the onset by myriads of shadows. Therefore, when a single opacity appears, or at the most two or three, it is a unique phenomenon that warrants immediate efforts to establish a histologic diagnosis. It is only by this means that an otherwise equivocal situation can be clarified so that specific treatment can be instituted and a more reliable prognosis given.

By following this concept at this institution, over 600 ambiguous problems of this type have been resolved: over 500 were found to have a new primary cancer (Fig. 1); 125 were solitary lung metastases originating in virtually all areas of the body and 12 had benign lesions.

When the malignant pulmonary tumors were resected, 36% of the metastatic group and 26% of those with primary lung cancer survived five years or more.[9]

When radiologic diagnoses were reviewed for this report, it was found that the presumption that a pulmonary shadow was a breast metastasis was correct 24% of the time (Table 2). These oft-repeated errors probably resulted from assumptions based upon seemingly incontrovertible evidence. For example, when a breast cancer and the lung shadow were synchronous, it seemed logical to assume that the shadow

TABLE 6. *Five-year Survival—Metastatic Group.*

Patient	Interval Breast and Lung Lesion (years)	Pulmonary Treatment*	Follow-up
HA 48 F	9	Chest wall resection + radium implant + ext. R.T.	16.5 years
MW 65 F	6	Wedge excision	9.5 years } NED
MB 45 F	3	Wedge excision	5.6 years
AK 57 F	Synchronous	Wedge excision	6.3 years - DOD
MP 56 F	5	Wedge excision	5.1 years - DOCWD**

* All had radical mastectomy (one bilateral), two had postoperative radiation therapy

** Perforated bleeding diverticulitis, breast cancer present

5 year survival - 31% (5/16)

MSKCC 11/73

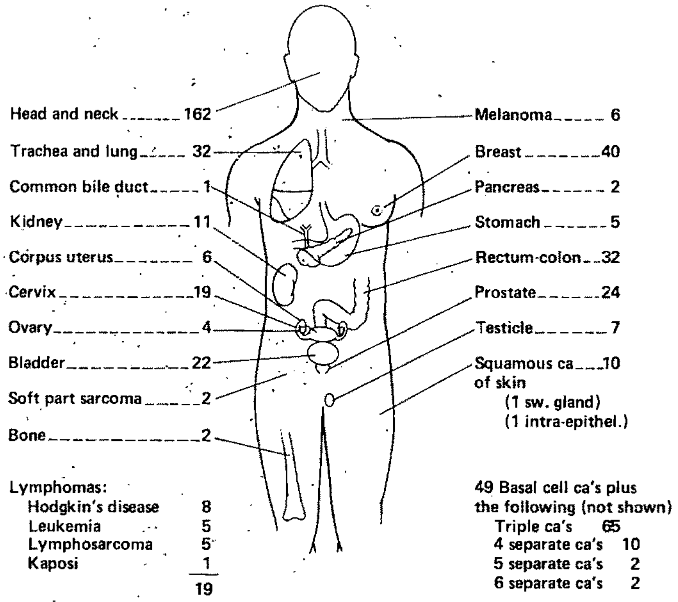

FIG. 1 Anatomic sites of 534 multiple primary cancers, one of which was lung (1933-1972 MSKCC).

was of mammary origin; this interpretation was also given when the shadow appeared 23 years later. Also on occasion, the shape, size and location of the opacity served to influence opinion enough so that a designation of a metastasis seemed most tenable at the time.

A diagnosis given by a radiologist to a clinician has weight and influence. Therefore, such statements should be made with caution. Both should acknowledge that a shadow is *not* a histologic diagnosis. In the specific conditions in question, this fact is of the utmost therapeutic importance: lung cancer is largely cured by surgery, whereas breast cancer metastases are managed by ablative surgery, irradiation, hormonal and/or chemotherapy. To resort to the latter regime by *presumption* may allow a curable cancer to become fatal.

The ambiguity of the exact nature of the pulmonary shadows can also occur at the microscopic level. Whereas it is easy to distinguish epidermoid or oat cell lung cancers from breast metastases, it is often difficult to be sure of this distinction when an adenocarcinoma is present because of the striking similarities that can exist between these two cancers.

To resolve this, comparison of the lung cancer sections with those of the original breast cancer is often rewarding. In addition, if the pulmonary lesion is in direct continuity with the adjacent bronchial epithelium and in particular, shows *in situ* carcinoma in its immediate vicinity, the tumor is believed to be of lung origin.

Special histochemical staining reactions to identify various types of acid mucopolysaccharide (mucus) production may be of some help. In metastatic breast carcinoma sections, the mucicarmine stain is often positive, whereas in bronchoalveolar carcinoma, it is negative.

The clinical course of the patient may also be influential in resolving this problem. If, for example, after excision of the pulmonary lesion, breast cancer metastases never appear, this could be interpreted as supportive evidence that the nodule was of lung origin. However, if showers of metastases become evident shortly after excision, this would favor the lung tumor as being a metastasis.

As mentioned previously, the interval between the breast cancer and the lung shadow cannot be used to indicate the probability of one diagnosis over another. This fact is well-documented in this study for in ten patients, when a shadow was concurrent with breast cancer, only one proved to be a metastasis; eight patients had new primary cancers of the lung and in one, it was a benign lesion. Although only one patient in this synchronous group is alive for five years or more, this is not truly representative of the potential value of aggressive therapy in this setting. It is quite possible that others may have survived had appropriate therapy been instituted rather than delay resulting from equivocation that occurred in the early cases.

In addition, the length of interval is not a reliable index of potential control for it was found that of four who survived five years or more, three had interludes that were less than 14 months and in one patient, it was eight years. Seven others had an interval over ten years but this fact did not result in any five year survivors in this group.

In three other patients because of evident widespread metastases, the pulmonary lesion was presumed to be a part of disseminated breast cancer. However, in all three, the cause of death at autopsy was found to be from primary lung carcinomatosis instead.

Similarly, in the breast metastasis group, among those who survived five years or more, one was synchronous and the others had three, five, six and nine year intervals from the treatment of their primary breast cancer.

In the metachronous group, the pulmonary shadows appeared from three months to 23 years later. Twenty-two of these proved to be metastases, one of which manifested itself 15 years after the breast primary. Thirty-five were new lung cancers and five were benign.

Management

It is a valid premise that the earlier a metastasis or a new cancer is detected and treated, the better the chance for cure. Therefore, it is necessary that all cancer patients have strict periodic and life-long vigilance.^{10,11}

The importance of such continual care is evident in this series in which half of the patients developed a pulmonary shadow five to 23 years after their primary breast cancer had been excised. This demonstrates that the usual guideline for cancer control, the so-called five-year cure can provide a false sense of security.

The optimum interval between examinations is, at best arbitrary but to some extent is determined by actuarial statistics. These show that the probability of metastasis or a new primary cancer is highest within five years after detection of the known malignant tumor (Table 1).

Consequently, for the first year, monthly examinations should be made: for the second year, bi-monthly, and after that, at least 3 or 4 times a year until the fifth anniversary has been reached. From then on, semi-annual examinations are maintained indefinitely.

Chest roentgenograms are essential to the care of the cancer patient as the lungs are common sites for primary tumors or metastases. Fluoroscopy should not be used for screening lungs as it is inadequate for detecting small opacities and is an impermanent record.[14] In this series, almost a third of the patients had a pulmonary shadow found by chance, the chest x-ray having been taken as part of a workup or routine followup examination. Therefore, it is recommended for heavy smokers and/or those who had radiation therapy over the chest (both well known carcinogens), that for the first postoperative year, a posteroanterior and lateral chest x-ray should be done every three months. However, in all patients, chest x-rays should be taken semi-annually or sooner if symptoms warrant.

Once a pulmonary shadow is found, an orderly progression of roentgenographic studies should be made. These include obtaining all previous chest x-rays for comparison; stereoscopic views in the posteroanterior and occasionally, in the lateral projections; tomograms to delineate equivocal shadows and uncover otherwise invisible opacities, and barium opacification of the esophagus with chest fluoroscopy to search for mediastinal and other abnormalities.

Additional radiographic studies such as a skeletal survey and laboratory tests are done in order to determine whether metastases are present. However, although some clues are afforded by chemistries, scans (liver, brain and bone) and selective celiac and superior mesenteric arteriograms, they are not, of themselves, totally reliable indices of the presence or absence of metastases having often been misleading in both directions.[15] As a consequence, it is unwise to decide upon a course of action based solely upon one laboratory finding; instead, all studies should be evaluated in the clinical context.

Bronchoscopy to obtain washings and/or a biopsy is recommended especially for those whose symptoms suggest bronchial involvement,[3] for centrally-placed lesions and for peripheral shadows that are 2 cm or larger. Cytologic studies often afford a good clue as to the nature of the lung lesion. In a study of pulmonary metastasis, in 12 patients, the diagnosis was established by cytology.[3] In addition, the probability that a new primary lung cancer is present makes it mandatory to do it. Exfoliated cells in sputum and/or bronchial washings can help distinguish the nature of opacities when there is a distinct histologic difference; e.g., epidermoid carcinoma of the lung and adenocarcinoma of the breast.

Scalene node biopsy is done if a mass is palpable in the area; mediastinoscopy and aspiration biopsies are performed in selected clinical situations but none of these is routine.

These preliminary studies take a few days to complete. If the diagnosis remains in doubt and if, in the aggregate, there is no suggestion of uncontrollable carcinomatosis, an exploratory thoracotomy should be done.

Surgical Management

In these settings, and subject to the patient's general condition, the extent of pulmonary resection depends upon the site and size of the lesion. At exploratory thoracotomy, if the lesion is peripheral, a wedge or segmental resection for diagnosis is performed initially. If it proves to be a new primary lung cancer, a lobectomy, preferably radical in type[4,13] is indicated. If the malignant lesion involves the main stem bronchus or extensively invades more than one of the major lobes, a radical pneumonectomy is completed. These radical procedures are recommended for several reasons. If a primary lung cancer is present, it is notorious for metastasizing to regional lymph nodes. Then, also as has been mentioned, if an adenocarcinoma is found on the initial pulmonary biopsy, it is often difficult to be sure as to whether it originates there or if it is a secondary breast deposit. In addition, a breast cancer metastasis in lung can, in turn, metastasize to the regional lymphatics; their inclusion in the resection makes for a more complete cancer operation.

However ideal the above suggestions may be, wedge excisions alone have value and may be indicated if the pathologist feels that the lung lesion is unequivocally of breast origin. In any event, it should be accompanied by regional lymph node biopsy.

For poor risk patients, these limited procedures can also be done. Then supplemental radiation and/or chemotherapy can be given for residual disease.

As there were ten patients who had synchronous breast and lung lesions, the problems peculiar to their management should be discussed. The first decision is one of priority of operation: which tumor should be treated first? Logically, the more malignant of the two deserves prior attention, however, the relative degree of malignancy is difficult to estimate at times for, the exact nature of the pulmonary neoplasm can even resist preoperative microscopic definition.

By and large, common sense should prevail. In general, since cancer of the lung is more lethal than that of the breast, the higher priority should be given to the lung opacity. But if the breast and lung lesions are ipsilateral and the patient is in good general condition, one may perform both procedures at the same time.

There is some reason to believe that performing surgery of the lung first may provide an advantage; namely, the findings may modify the breast treatment. If, for example, the suspected solitary opacity reveals innumerable pulmonary breast cancer metastases instead, the subsequent breast surgery may be limited to a biopsy. Or, if an oat cell carcinoma is found, because it is notoriously lethal, less aggression may be shown in the treatment of the breast lesion.

On the other hand, if the shadow proves to be a new primary lung cancer, a solitary metastasis or a benign tumor, a more energetic approach in treating the breast cancer should be pursued.

Multiple cancers in the same patient are no longer considered to be an oddity. Therefore, one must be alert to the possibility of a cancer patient developing new primaries. More specifically, we can look forward to seeing more of the combination we described as more females are surviving their breast cancers and the rate of lung cancer in women is rising precipitously. Therefore, the synchronous or metachronous occurrence of an opacity should spur immediate and energetic activity to make a correct diagnosis, for it is only by this means that specific treatment can be instituted and a more accurate prognosis given.

Acknowledgments

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Human Tissue Reaction to Sutures

R. W. POSTLETHWAIT, M.D., D. A. WILLIGAN, D.V.M., Ph.D., ALEX W. ULIN, M.D.

Tissue reaction to sutures was studied in 666 specimens obtained from patients from one day to 23 years after operation. Reaction to catgut depends on the stage of absorption and is mainly histocytic in type. Nonabsorbable sutures are encapsulated by a rim of connective tissue, while near the suture histocytes, giant cells and lymphocytes are found. This is most marked with silk and cotton, less so with Dacron, and least with nylon and wire. Tissue infiltration into the suture interstices is variable. The reactions resemble the findings in experimental animals.

A NUMBER of reports[1-9] have described the tissue reaction to sutures in experimental animals, but to our knowledge, no systematic study of these reactions in humans has been performed. We believe such a study is of interest of itself and also to aid in interpretation of animal investigations as applicable to patients.

Methods

The material was obtained at a second operation on patients or at autopsy. A small block of tissue to include at least part of the suture was removed, fixed and stained with hematoxylin and eosin. Considerable care was taken in orienting the tissue so that a cross section of the suture and adjacent tissue would be secured.

The microscopic findings were first described by one of us. Independently, another one of the authors graded the tissue response to the suture, on a scale of 0 to 4, for tissue infiltration into the suture strands and the approximate number of the following cells: neutrophils, lymphocytes, fibroblasts, histiocytes, and giant cells. As shown in Table 1, 14% of the 666 specimens were not satisfactory for grading. In a number of instances, this was due to hemorrhage or infection in the area of the suture. Wire was, of course, removed from the tissue before sections were cut, and grading was done only when the site of the wire could be identified unequivocally.

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The number of sutures of each type is shown in Table 1 and the interval the suture had been in the tissue in Table 2. The longest intervals, in years, for each suture was catgut 11, silk 23, cotton 7, wire 33, nylon 10, Dacron 11, and Dacron coated with Teflon 6. Sutures were obtained from a wide range of sites in the body but 80% came from muscle, fascia, or skin.

Tissue Reaction

The initial reaction of the tissues is a reflection of the amount of injury inflicted by passage of the needle and suture. Assuming the same technique, tissue, and other reactive factors such as absence of infection, the reaction will be the same for all sutures during the first five to seven days, if not longer. The following descriptions, therefore, concern the chronic rather than the acute response of tissues to sutures.

Catgut

After the initial reaction subsides, catgut appears the same as any monofilament suture with a thin connective tissue capsule, a few histiocytes and lymphocytes. The reaction is altered when absorption begins, the time of absorption being variable. The absorbing cells may remain primarily at the periphery of the suture or clefts may appear in the catgut into which the cells infiltrate. The cells are almost exclusively monocytic with a few lymphocytes and few or no polymorphonuclear neutrophils. Capillary formation is variable and no eosinophilic reaction is seen as occurs occasionally in animals. After absorption is complete, the site is marked by a collection of monocytes with characteristic brown, foamy cytoplasm.

A wide range of apparent biologic variation exists in the time of absorption as demonstrated by the catgut sutures removed, one at eight and the second after 11 years.

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Table 1. *Human Tissue Reaction to Sutures: Source of Material*

	Sutures Graded				
	Surgical	Autopsy	Total	Not Graded	Total
Catgut	12	16	38	18	46
Silk	224	116	340	50	390
Cotton	2	2	4	0	4
Wire	13	2	15	22	37
Nylon	39	54	93	17	110
Dacron	23	11	34	7	41
Dacron-T	27	10	37	1	38
Total	340	211	551	115	666

Table 2. *Interval Graded Sutures in Tissues*

	<1 Year	1–5 Years	6–10 Years	>10 Years
Catcut	26	0	1	1
Silk	199	103	24	14
Cotton	1	2	1	0
Wire	7	4	2	2
Nylon	78	13	2	0
Dacron	24	7	2	1
Dacron-T	25	8	4	0
Total	360	137	35	19

Both were surrounded by a connective tissue capsule with no evidence of absorption.

Silk

The reactions to silk may be divided into two major types. In the first and most frequent, the suture remains compact and is surrounded by a fibrous tissue capsule of variable thickness. Within the capsule adjacent to the suture a layer of histiocytes is seen, usually from one to three cell layers deep. Giant cells vary in both occurrence and numbers. Lymphocytes also vary and occasionally occur as focal accumulations. In the more cellular reactions, capillaries may be prominent. In the second type of reaction, the capsule is present but the interstices of the suture are invaded by fibroblasts and histiocytes. In rare instances, the reaction appears much like a granuloma.

From clinical experience, silk is known to be absorbed and evidence of this was found in this study. A few sections were seen in which only four or five strands of silk remained, the site characteristically showing a fairly brisk monocytic reaction. Another point of interest was those situations in which a loop of suture could be reasonably well identified. On the side of the suture toward the tension, acellular fibrous tissue was present while the cellular reaction was opposite the direction of tension.

Cotton

Only a few specimens of cotton were obtained. The reaction was quite similar to silk but somewhat more cellular.

Wire

The spaces left by wire are surrounded by a fibrous tissue capsule, all or a part of which is lined by monocytic cells. The reaction is considerably less than silk. The spaces tend to be oblong or eccentric, suggesting a cutting action.

Nylon

The tissue reaction to nylon is the least of all sutures examined. All specimens contained the monofilament type, and this is surrounded by a narrow, compact fibrous tissue zone. Histiocytes adjacent to the suture occur occasionally; giant cells rarely. No fragmentation of the suture is seen.

Dacron

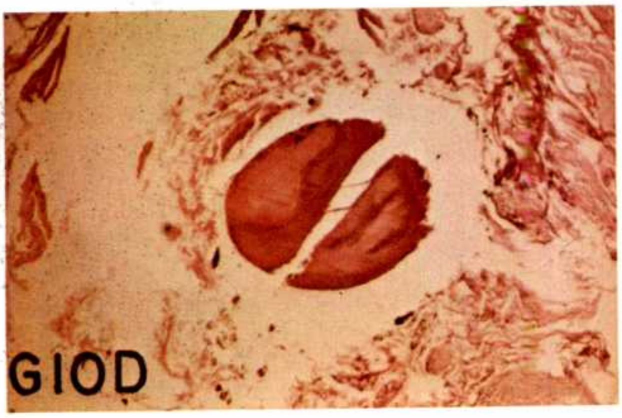
The tissue reaction to this material is very similar to that seen to silk except overall the reaction is considerably less. The suture usually remains compact, the fibrous tissue capsule is lined by histiocytes, and giant cells may be present. Invasion between the suture strands does occur and this is more likely to develop after longer periods of implantation.

Dacron Coated with Teflon

This material elicits a response similar to Dacron with the additional reaction due to what apparently is Teflon shed off the Dacron. In the sections, this brownish amorphous material may remain in or near the suture, stimulating a greater cellular response. In a number of specimens, however, the Teflon is seen as scattered granules in the vicinity of the suture, each particle being surrounded by its own histiocytic and giant cell reaction.

→

Fig. 1. (Overleaf, from left to right and above down) *G10D*, Gut 10 days, gastroenterostomy. Essentially no reaction. *G19D*, Gut 19 days, subcutaneous. Absorption beginning, mainly by monocytes. Serrations at edges and one cleft in suture. *G20D*, Gut 20 days, subcutaneous. No absorption; fibrous capsule and little cellular response. *G42D*, Gut 42 days, fascia. Fragmentation of suture with monocytic reaction. *G1Y*, Gut one year, fascia. Brown, foamy remnants in cells. *G11Y*, Gut 11 years, vaginal cuff closure. No absorption or reaction. *S55D*, Silk 55 days, chest wall. Two characteristic reactions in same patient. *S55D*, Fibrous capsule with moderate cellular reaction around compact suture. *S55D*, Tissue infiltration among silk fibers. *S82D*, Silk 82 days, esophagogastric anastomosis. Part of loop: acellular fibrous tissue at top in direction of tension. *S3Y*, Silk 3 years, joint capsule. Probably a knot. Fibers of silk scattered throughout tissue with granulomatous appearance. *S6Y*, Silk 6 years, fascia. Number of fibers indicates absorption. *S6Y*, Silk 6 years chest wall. Thick fibrous capsule; monocytes near suture. *S12Y*, Silk 12 years, abdominal wall. Mature capsule but still some cellular reaction. *S20Y*, Silk 20 years, fascia. Thick capsule, fairly cellular with monocytes and giant cells near suture. *C2Y*, Cotton 2 years, fascia. Reaction at opposite poles. (Low power × 40; high power × 100)



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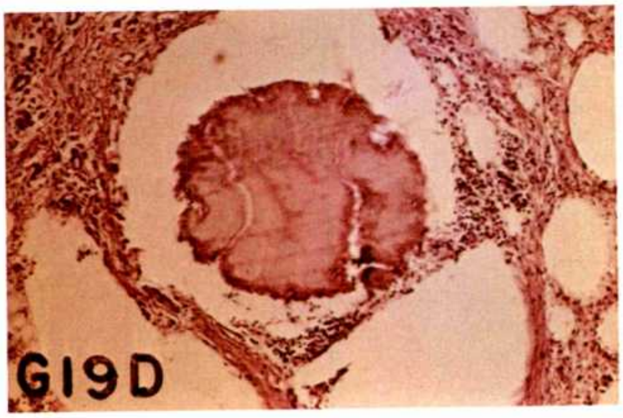

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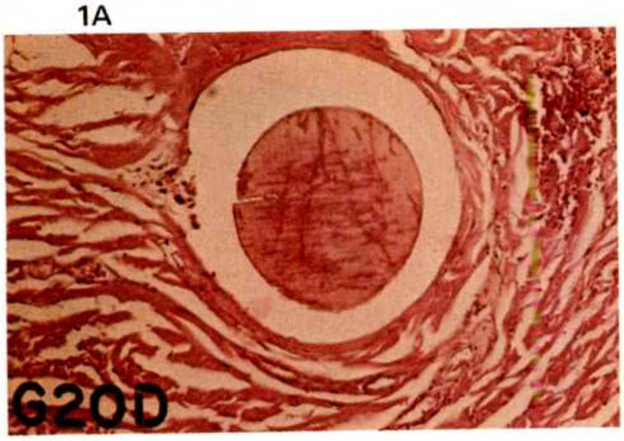

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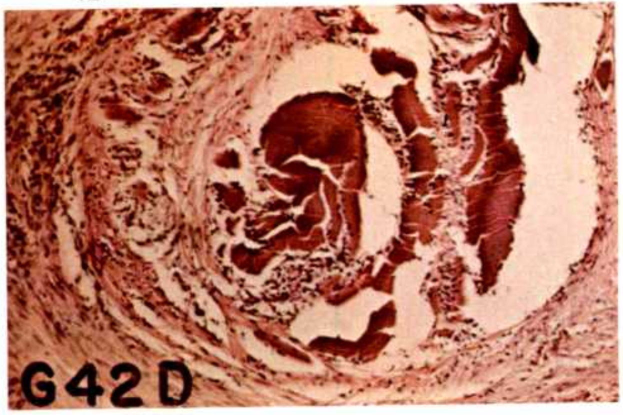

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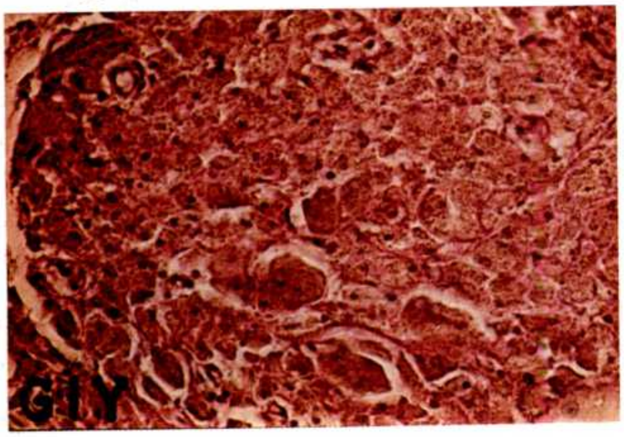

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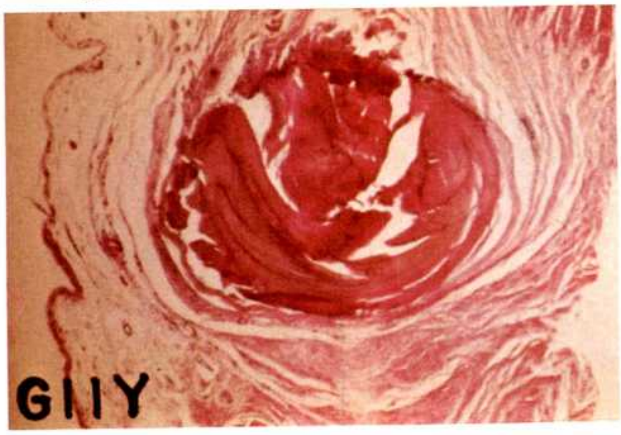

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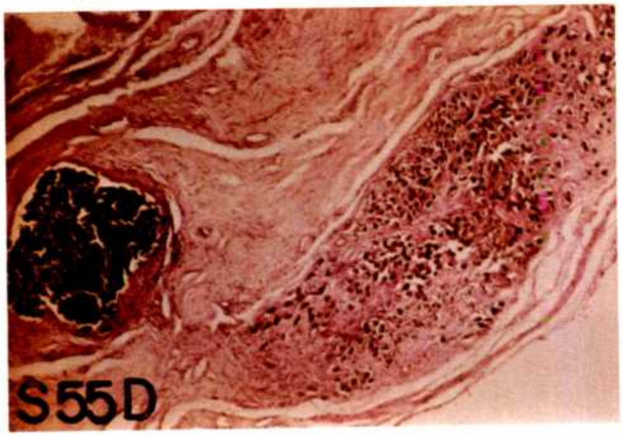

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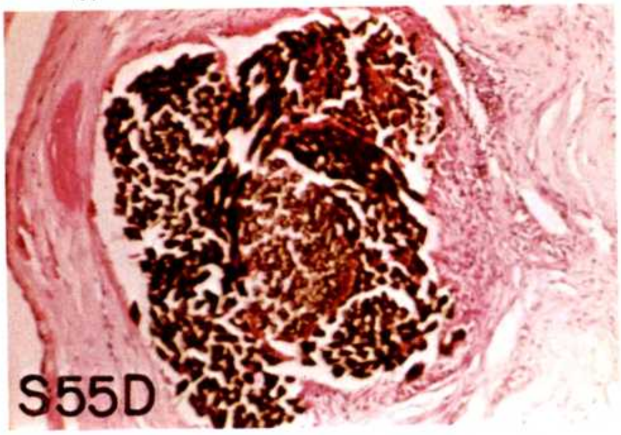

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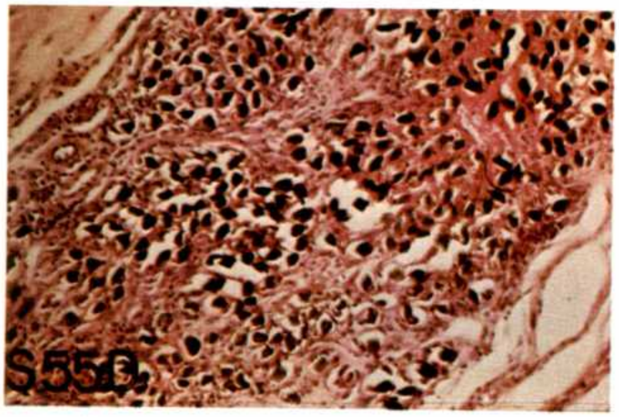

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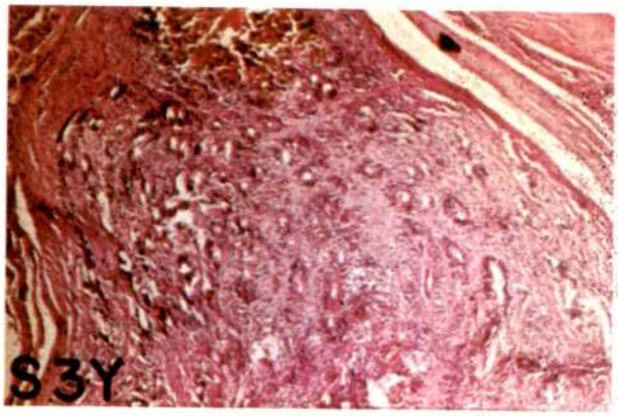

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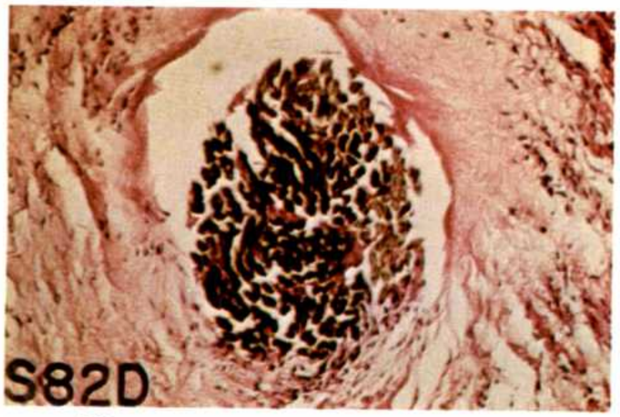

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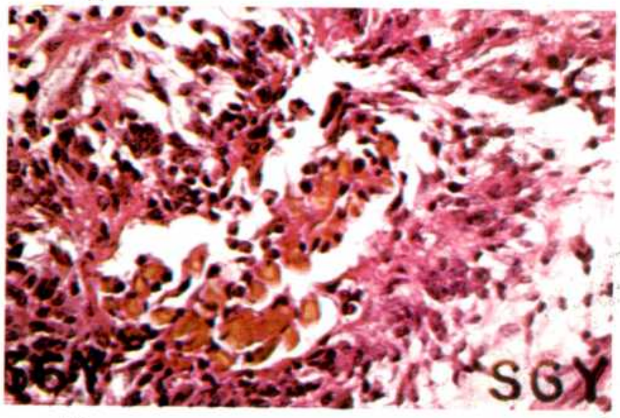

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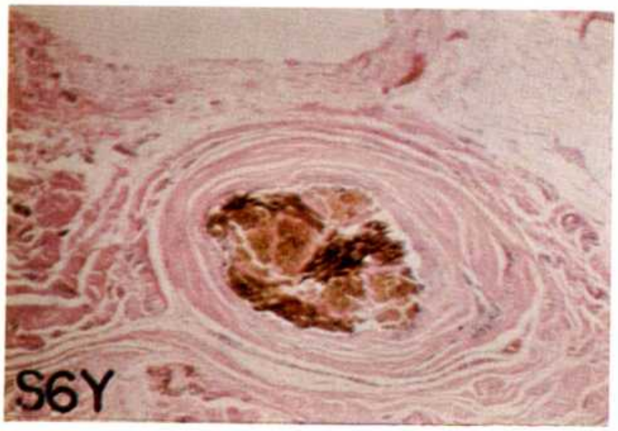

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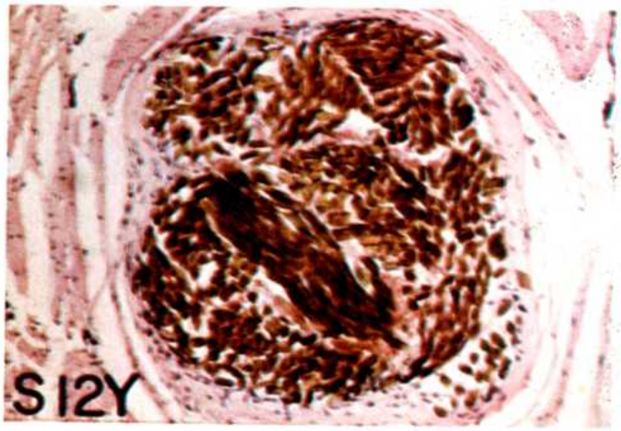

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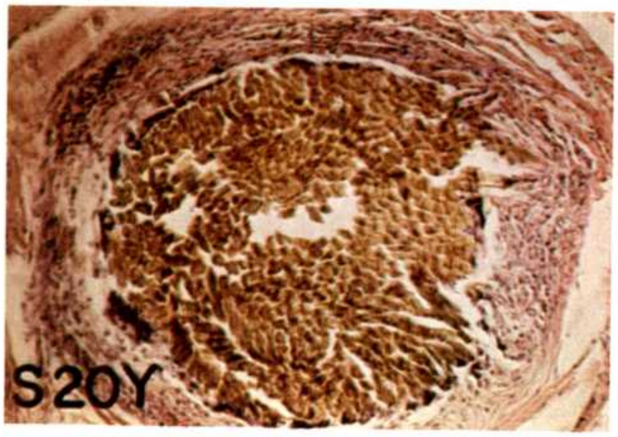

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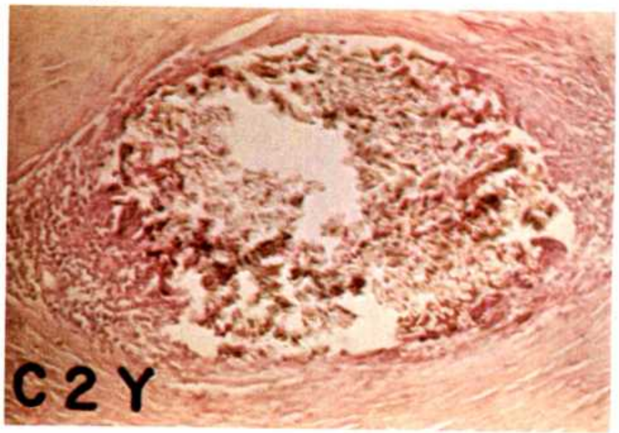

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TABLE 3. *Grades of Tissue Reaction*

	No. Sutures	Neutro-philes	Lympho-cytes	Fibro-blasts	Histio-cytes	Giant Cells	Invasion Suture
Silk 3 wks.–1 Yr.	110	0.16	1.0	2.3	2.0	0.9	0.9
Silk >1 Yr.	141	0.12	0.8	2.6	2.0	0.9	0.8
Nylon >1 Yr.	15	0.0	0.6	1.1	0.4	0.1	0.0
Dacron >1 Yr.	10	0.0	0.8	2.0	1.6	1.2	1.2

Miscellaneous

Suture specimens were obtained from 12 renal transplant patients. All were receiving azathioprine and, most of them, steroids. Catgut, silk, nylon and Dacron were examined. The transplant had been less than 30 days earlier in four patients and ranged from two months to five years in the others. The remarkable finding was the very limited response, either fibroblastic or histiocytic, to the sutures. Actually, in some sections the suture appeared to have displaced adjacent normal tissue without any cellular response.

Discussion

In previously reported animal studies of tissue reaction to sutures, one of us[8,9] has utilized a system of grading the reaction entailing the size of the reaction zone, the type of reactive cells, and an estimate of their number. Although a numerical grade is then obtained, the grading process is tedious and the grade of value only for comparison. In the present study, a less detailed system of grading was used and no exhaustive analysis was made of the results. Grading, however, is useful as illustrated by Table 3. The reaction to silk in place from three weeks to one year is compared to silk in tissue over a year. The grades indicate that little change occurs with time for the silk sutures examined. Comparing silk with nylon and Dacron indicates the least reaction is seen to nylon, a more intense reaction to Dacron, and still greater reaction to silk.

The tissue reaction to sutures has been reported in detail in the rat, rabbit, and dog. The reaction in rats to various sutures appears to be more severe than that in the rabbit or dog.[3,4] Our work previously has been almost exclusively with rabbits. Although a precise comparison cannot be made, the reaction in humans generally is similar to but less intense than that seen in experimental animals. Transfer of the findings in animal studies would, therefore, appear to be acceptable with only moderate limitations.

Unfortunately, the specimens available did not include some of the more recently developed sutures, both absorbable and nonabsorbable. Reports of animal studies concerning these are available, however, and it is apparent that the ideal suture remains to be found.

Parenthetically, in spite of the long exposure to suture material in some of the patients, no evidence of neoplasia was seen in any section.

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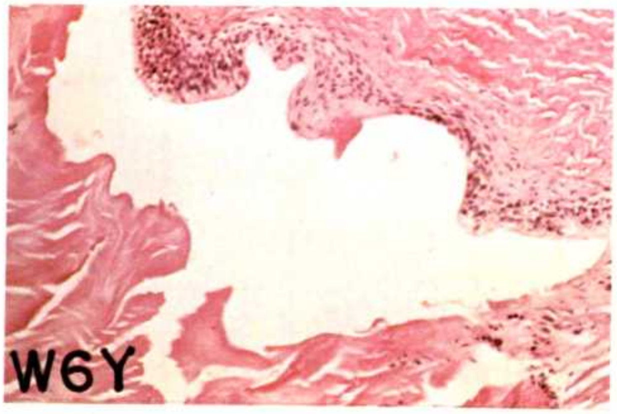
FIG. 2. (Opposite and overleaf, from left to right and above down.) *W6Y*, Wire 6 years, fascia. Very moderate cellular reaction along one side. *W8Y* Wire 8 years, fascia. Fibrous capsule with flat monocytes lining. *N10D*, Nylon 10 days, subcutaneous. No reaction. *N2Y*, Nylon 2 years, tendon. Unusua uniform lining of monocytes. *N10Y*, Nylon 10 years, fascia. Essentially no reaction. Note physical change in staining of suture. *D7M*, Dacron 7 months chest wall. Fibrous capsule with monocytes near suture. *D40M*, Dacron 40 months, fascia. Fairly thin capsule; cellular reaction persists with few giant cells. *D11Y*, Dacron 11 years. Still encapsulated but septa of fibrous tissue. Note giant cells. *T3M*, Teflon coated Dacron 3 months, fascia. Cellula reaction in part due to shed Teflon. *T55W*, Teflon coated Dacron 55 weeks, subcutaneous. Dark cellular areas away from suture surround brownish amorphous material thought to be Teflon. *T55W*, Higher power of previous section. Note area of reaction in left upper corner. *T6Y*, Teflon coated Dacron 6 years, fascia. Shed Teflon persists in and near suture. *D22D TR)*, Dacron 22 days, kidney transplant. No reaction. *S12D*, Three sections of silk 12 days skin. Epithelial down growth along suture; note keratin formation.



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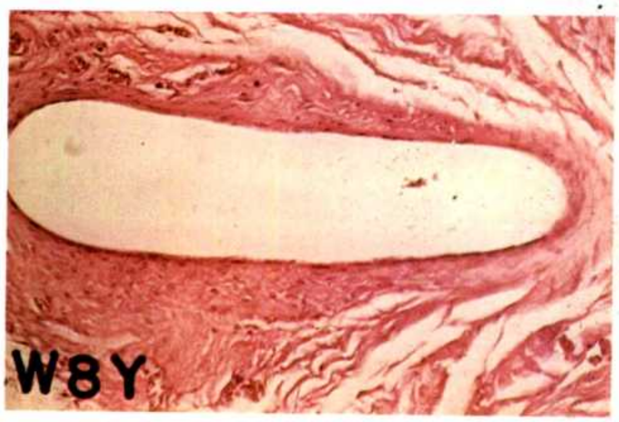

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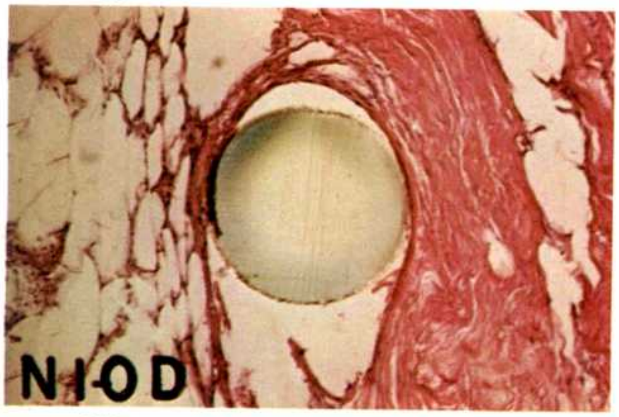

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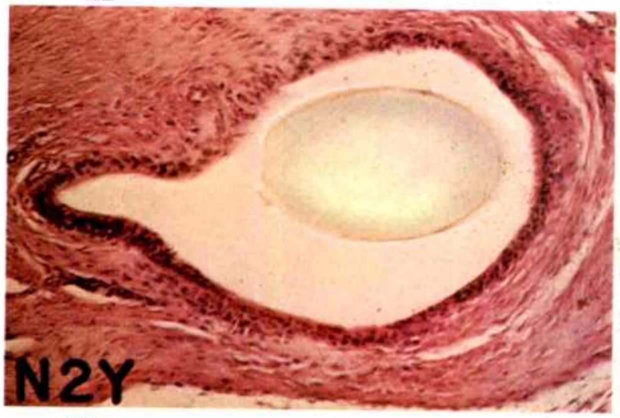

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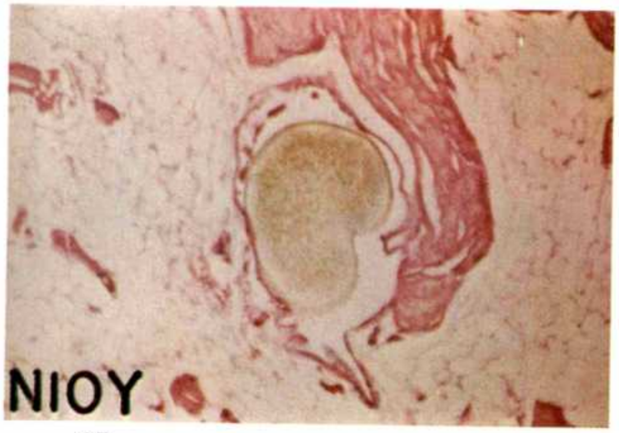

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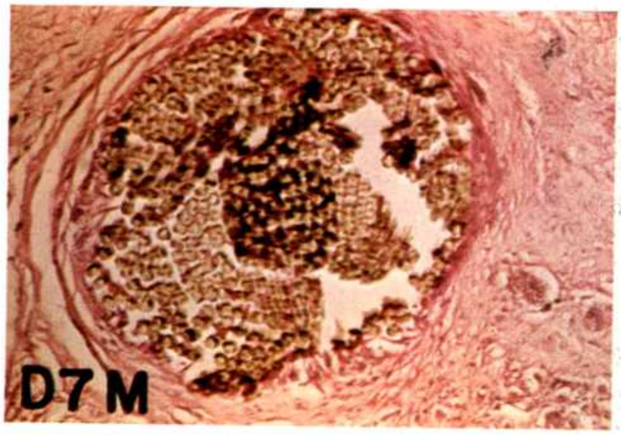

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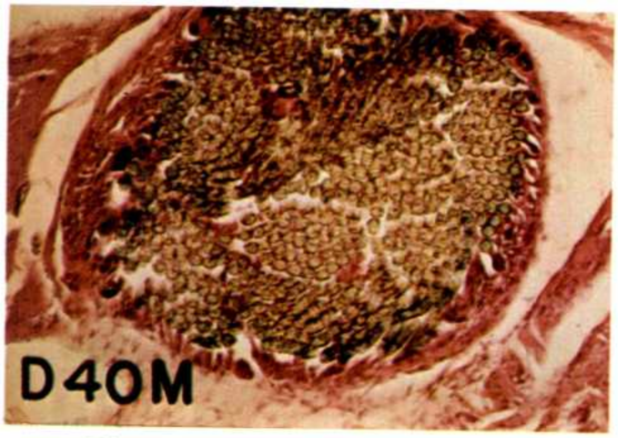

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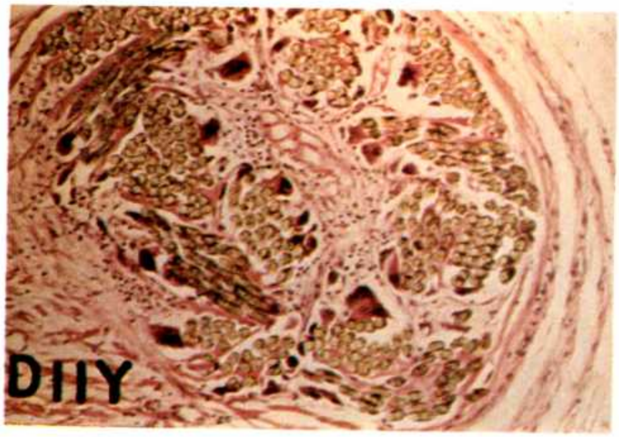

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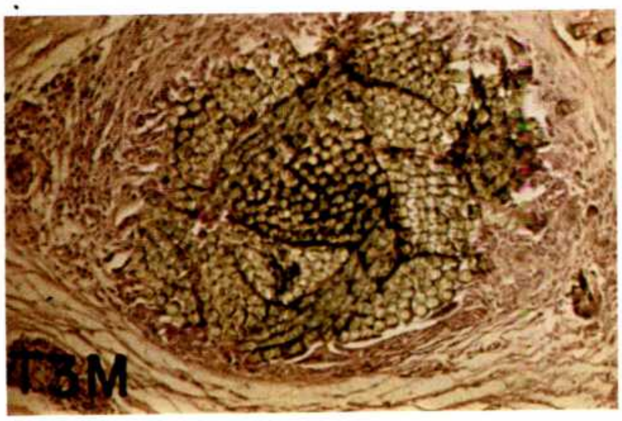

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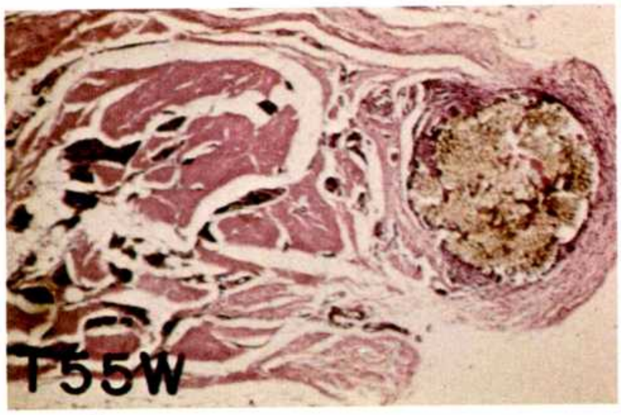

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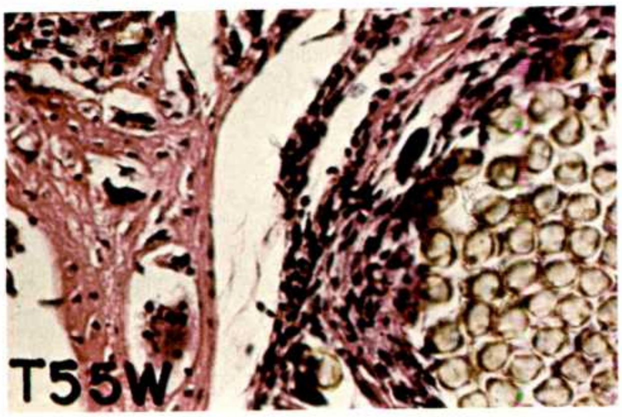

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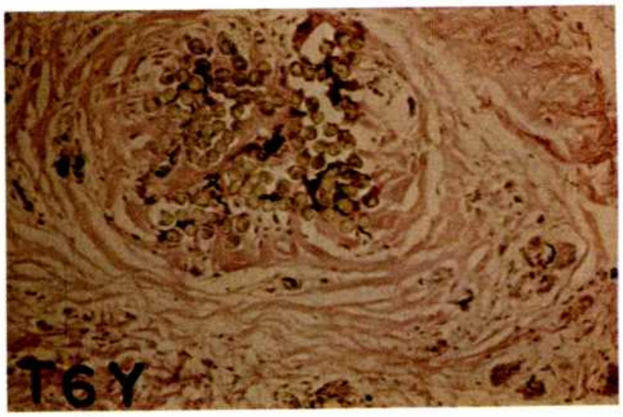

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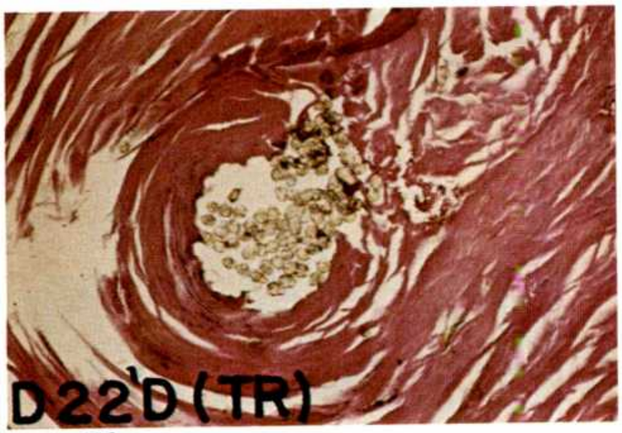

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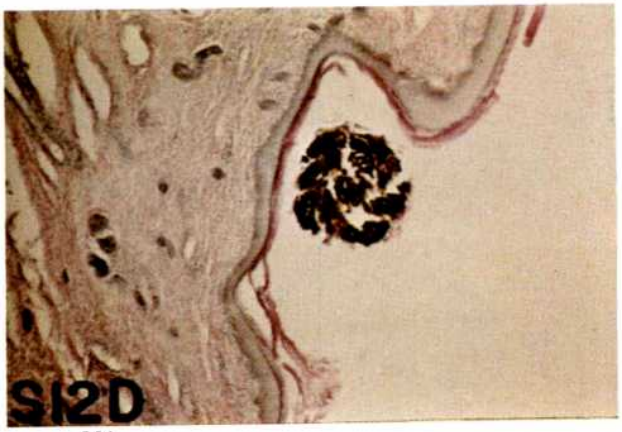

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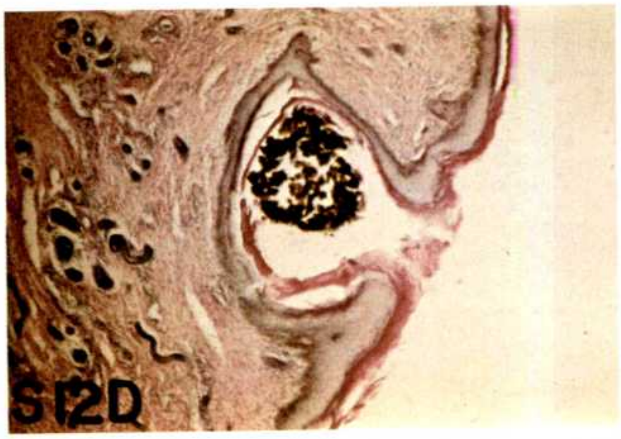

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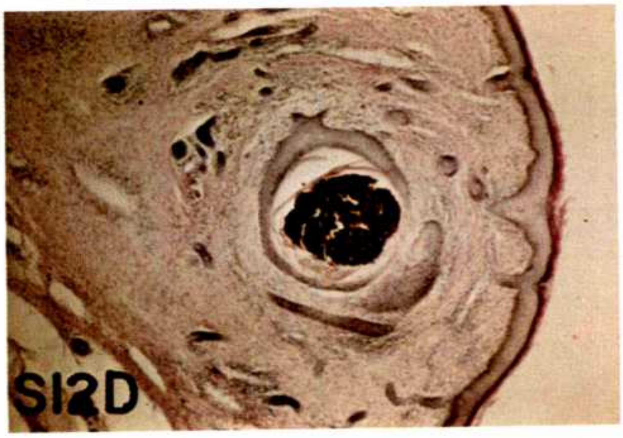

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What is Clinical Smoke Poisoning?

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In this 13-year study, 51 patients were admitted with the primary diagnosis of "smoke poisoning," "carbon monoxide (CO) poisoning" or "respiratory burns." Forty patients (78%) had diagnosis of smoke poisoning with minor or no skin burns. The study indicated that clinical diagnosis of CO poisoning cannot be made reliably without carboxyhemoglobin (COHg) determination and that smoke poisoning patients often had CO poisoning. Seventeen of 19 smoke poisoning patients (89%) had CO poisoning above COHb levels of 15% saturation. Carbon monoxide was successfully removed from the blood by improving alveolar ventilation and oxygen concentration. However, there were 2 smoke poisoning deaths as the result of gaseous chemical injury. There was a correlation coefficient of 0.87 between initial COHg levels and patients' hospital days primarily determined by patients' pulmonary complications. Since CO is non-irritating, COHb levels may be used as an additional indicator of suspected pulmonary injury by noxious combustion gases.

THE SCIENTIFIC DEFINITION of smoke and the medical meaning of "smoke poisoning" or "smoke inhalation" are not well understood. The purpose of this paper is to attempt to define more specifically "clinical smoke poisoning" as we now understand it. "Respiratory burn" pathophysiology has been described earlier.[22]

In 1962 Phillips and Cope[10] labeled respiratory tract damage as a "principal killer" in burn victims. In 1967, Stone reported "respiratory burns" in 15% of 197 patients some of whom may have had concomitant smoke poisoning.[18] Because of recent recognition and difficulty in differentiation between respiratory burn and smoke poisoning, there have been no available clinical statistics concerning incidences of the two conditions or the incidence of their coexistence.

Smoke poisoning and/or asphyxia was the primary cause of death in 30% of all fire fatalities in New York City during the years 1966 and 1967.[23] Respiratory tract involvement was found in 70% of deaths under 12 hours and in 46% of victims who survived more than 12 hours. 53.5% of 185 victims who survived less than 12 hours had smoke poisoning and/or asphyxia as the only cause of death. Significantly, 79% of those having primary diagnosis of smoke poisoning and/or asphyxia had actual carbon monoxide poisoning. Twenty-four per cent of these patients had lethal levels of CO (above 50% carboxyhemoglobin saturation).[23]

Since almost one-third of fire fatalities are due to smoke poisoning, and for many years to come combustion will remain the main source of energy, we must regard smoke and fumes of combustion as major threats to life. Therefore, it behooves us to understand better the acute clinical "smoke poisoning" which in turn may help our understanding of the subtle chronic effects of air pollution and cigarette smoking. Through a better understanding of "smoke poisoning," we may find effective and expeditious methods of treatment and prevention.

Materials and Methods

In the 13-year period 1960–1972, 51 patients were admitted with the primary diagnoses of "smoke inhalation," "CO poisoning" or "respiratory burns." Patients whose main problem was their body surface burns were not included in this study. Thirty of these patients were admitted during 1960–1970 and 21 patients in the two years thereafter. Their records were evaluated critically with respect to admission diagnoses, laboratory analyses, hospital course and treatment.

Results

These 51 patients were admitted through the emergency services of Columbia-Presbyterian Medical Center. Forty (78%) fell in the category of "smoke poisoning" on the basis

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PRIMARY CLINICAL DIAGNOSIS	CASES	BSA BURNS		CLINICAL EVIDENCE OF LATE SEQUELAE		LABORATORY DIAGNOSIS OF CO POISONING	DEATHS
		Subjects % burn	Average % burn	Neurologic	Pulmonary		
SMOKE POISONING	40	3 % 1 % 10 % 10 % 15 %	0.97	1	6	16	2 [2 days and 12 days]
CARBON MONOXIDE POISONING	6	0	0	3	0	1	1 [7 hours]
RESPIRATORY BURN	5	30 % 20 % 5 % 4 % 3 %	12·4%	0	2 [no follow up in 1]	0	2 [4 days and 8 days]
TOTAL	51		2%	4	8	17	5

FIG. 1. Clinical results 1960–1972 of primary inhalation injuries.

of having been exposed to the smoke of a fire with minor or no body burns. There were six primary clinical diagnosis of carbon monoxide poisoning and five patients with the primary diagnosis of respiratory burns by examination. The ages of these patients ranged 6–76 years and there were 37 males and 14 females (Fig. 1).

During the decade of 1960–1970 there was no blood carbon monoxide determination because emergency room equipment° for the test was not available. With the availability of a quick laboratory determination in the 2-year period that followed (1971–1972) all 21 patients admitted for possible inhalation injuries from a fire were tested for carbon monoxide poisoning.

Clinical diagnosis of CO poisoning without the help of blood CO determination was made in 5 patients during 1960–1970 primarily on the basis of history and neurologic sequelae. It is interesting to note that clinical diagnosis of acute CO poisoning was made on the basis of cherry-red skin in only one patient before the laboratory report of a blood CO saturation of 51%. Whereas 17 of 21 (80%) had acute CO poisoning at above 15% carboxyhemoglobin saturation during 1971 and 1972.

This study also shows that where clinical diagnosis of "smoke inhalation" or "smoke poisoning" is made, if blood CO level is determined, 16/19 (84%) will reveal some degree of carbon monoxide poisoning (CO saturation above 15%). Nine patients had carboxyhemoglobin saturation of 29% or more.

Ten patients (20%) had sustained burns of face, upper trunk and extremities. Their burns were mostly 1st and 2nd degree burns. Patients with the primary diagnosis of smoke poisoning had an average of 0.97% body burns whereas respiratory burn patients had an average of 12.4% body surface burns. Only one of these patients had a third degree burn necessitating a small skin graft (Fig. 1).

Ten patients (25%) with the primary diagnosis of smoke poisoning and all 5 patients with the diagnosis of respiratory burns had some visible evidence of respiratory tract injury ranging from erythema and blisters of the orophyarynx to congestion and edema of the tracheobronchial tree as observed by direct or indirect laryngoscopy or broncoscopy. In only three patients did the initial chest X-ray reveal pulmonary edema. Although only three admission chest X-rays showed initial pulmonary changes, a total of 11 patients (28%) developed either pulmonary edema or X-ray evidence of pneumonitis during their hospitalization. The rest of the patients were treated for atelectasis, probable pneumonitis or bronchitis on the basis of fever and their chest physical findings.

Since 1970, the mode of initial respiratory resuscitation has been influenced greatly by the admission arterial blood gases and CO determinations. Six patients required MA-1 respirator; three resuscitation via tracheostomy, and in three patients, nasotracheal or orotracheal tubes were used. Seven patients were treated with IPPB, five of whom required tracheostomy. The remaining cases received humidified oxygen by nasal catheter or oxygen tent for varying periods of time.

Fourteen patients were placed on prophylactic antibiotics, usually penicillin, though ampicillin, keflin and tetracycline were also utilized. An additional six patients developed significant pulmonary infection requiring specific antibiotic therapy.

Ten patients were treated with bronchodilators, and three patients required digitalis and or diuretics for delayed pulmonary edema and congestive heart failure in elderly patients. Eight patients of 40 smoke poisoning and one patient out of five respiratory burn and none of the CO

° CO-Oximeter, Instrumentation Laboratory, Inc., Watertown, Mass 02172.

poisoning patients received corticosteroids. The steroids were given in 2–4 divided doses within the first 24–48 hours only.

The overall mortality was 9.8%, five patients: 3 cardiorespiratory arrests and 2 with intractable pulmonary edema (4 days post injury) and overwhelming pulmonary infection (12 days post injury) respectively (Fig. 1). There were two deaths in 40 smoke poisoning patients, one death in six carbon monoxide poisoning and two deaths in five respiratory burns.

The carbon monoxide clearance from the blood was followed with serial determinations of carboxyhemoglobin levels. The two patients who had the highest CO levels, 82% and 51%, both on MA-1 respirators with 100% O_2, had rapid clearance of CO from the blood within four hours. Those patients who had CO levels below 30% were treated fairly effectively with nasal oxygen and ventimask, bringing their blood CO levels to 10–15% within four hours (Fig. 2).

It is also interesting to note that most patients who were hospitalized for longer than 2 days had initial CO levels above 15%. There seems a definite relationship between the initial blood CO level and the patient's length of hospitalization (Fig. 3). The patient with 82% carboxyhemoglobin who died 7 hours after admission with fatal CO poisoning and another patient whose hospital stay was prolonged because of skin grafting were excluded in the calculation of correlation coefficient. The 0.87 correlation coefficient between initial blood CO levels and hospital days indicated a fairly good correlation between initial blood CO levels and pulmonary damage as well, since patients length of hospital stay was primarily determined by the degree of pulmonary complications as a result of exposure to smoke. Since CO is not noxious, and as we have shown in dog experiments,[20] does not cause pulmonary edema, the reason for this relationship may be nothing more than CO acting as an indicator of other gaseous exposure which is injurious to the lungs, but not detected in blood or other tissues. Therefore, we have clinically used carboxyhemoglobin levels as a possible index of pulmonary injury by other injurious gases which coexist with carbon monoxide in smokes of structural fires. Smoke poisoning patients who have clinical evidence of tracheobronchial tree or pulmonary injury and those patients without clinical evidence of such injury but who have carboxyhemoglobin levels of 20% or more, are usually hospitalized for observation for at least 24 hours if the blood CO determination was made within one hour of acute exposure to fire products. It must be pointed out that in many smoke poisoning patients evidence of pulmonary injury may not become clinically obvious until 12–48 hours. A chart has been constructed on the basis of clinical blood CO clearance curves and the experimental data. From such a chart one can interpolate the approximate blood CO levels at the time of exposure if the delay time and emergency blood CO determination are known (Fig. 4).

Discussion

Clinical

We believe that the significance and diagnosis of inhalation injuries in fire victims, by and large, have been underestimated and overlooked. The inhalation injury may be predominantly "smoke poisoning" without significant body

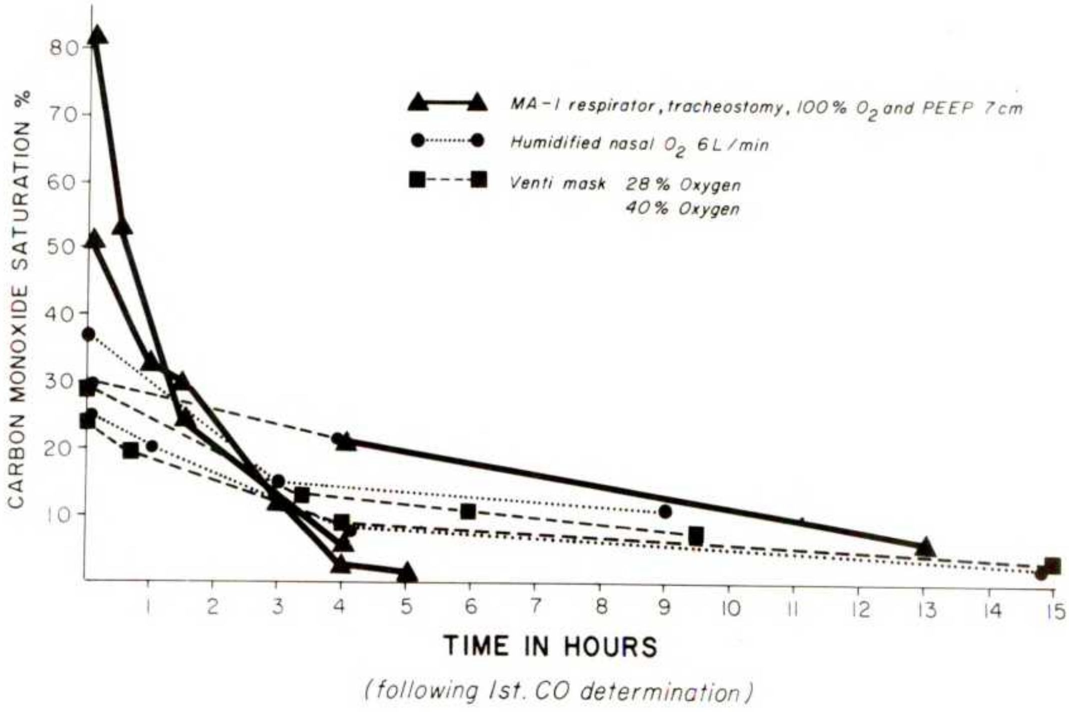

FIG. 2. Carbon monoxide disappearance in blood of smoke poisoning patients.

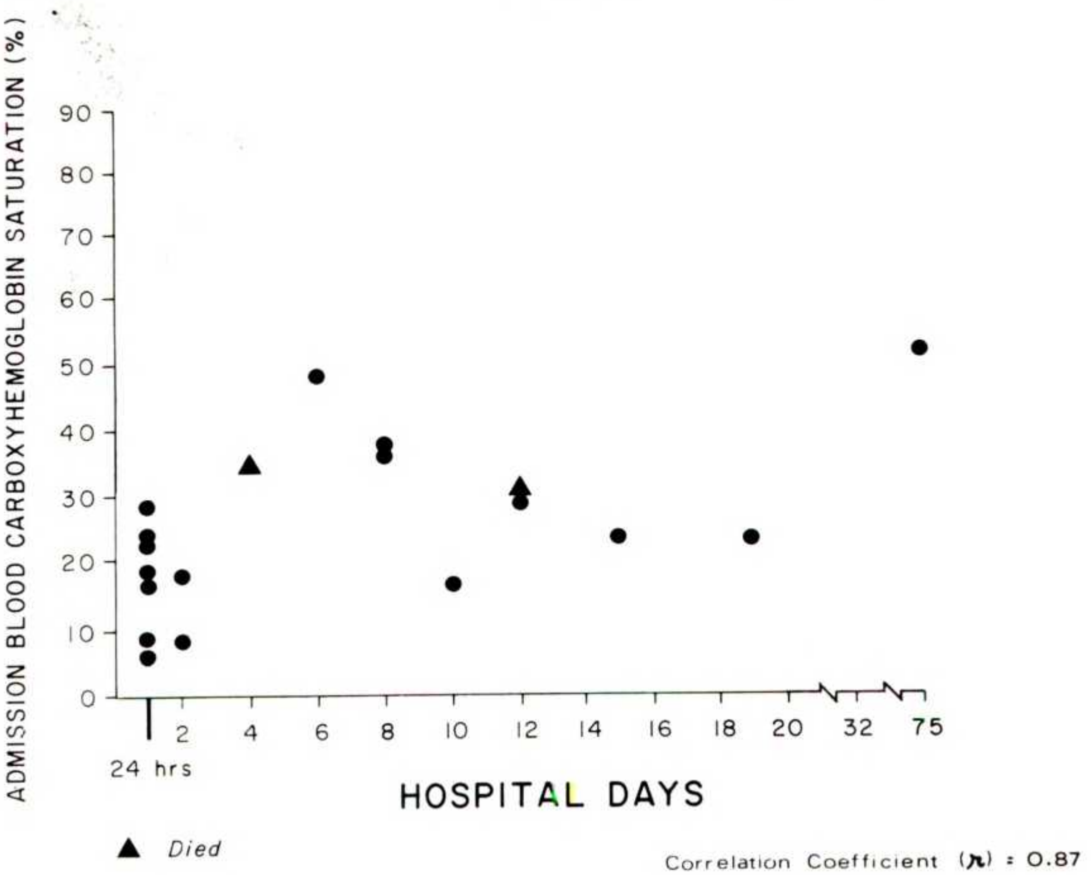

FIG. 3. Correlation of initial carboxyhemoglobin saturation and patients hospital stay based primarily on pulmonary complications.

surface burns and appears to be primarily a chemical injury to tracheobronchial tree and lung parenchyma. Such injury can extend to the peripheral respiratory tissues and rapidly emerge as dyspnea with wheezes and rales. Whereas in the "respiratory burn" occurring in patients with significant burns of anterior chest, neck, face, mouth and/or nose with singed vibrissae, the thermal energy seems to inflict the primary injury. This injury often is central, *e.g.*, involving upper respiratory tract, pharynx larynx, trachea and probably proximal major bronchi. Blood carboxyhemoglobin level may have no relevance in such primary injury. Pathophysiology of this type of injury has been described in another publication.[22] No doubt there are some patients who have a combination of chemical gaseous and thermal injuries to the respiratory tissues. The intention of this paper is to discuss the "smoke poisoning" as the primary injury.

From our studies it appears that the clinical smoke poisoning or "smoke inhalation" is often a chemical respiratory injury with concomitant carbon monoxide poisoning. This study shows that visible respiratory tract damage is seen in about 25% of smoke poisoning cases and in five out of five (100%) respiratory burn patients. Because of low specific heat of gases the thermal injury does not seem to proceed beyond the major bronchi,[9] whereas chemical gas injury easily reaches the alveolar level. It is thus interesting that most tracheostomies were done in respiratory burn patients for upper airway obstruction and in those with chemical injury of smoke poisoning, tracheostomy was done after prolonged intubation (longer than 5 days) and ventilatory support for patchy atelectasis, interstitial edema, and/or excessive secretions. There is no doubt that one should avoid doing tracheostomies when it is not absolutely necessary since it acts as an insult to injury.[21]

The study clearly points out as did the autopsy studies,[23] that clinical diagnosis of carbon monoxide poisoning on the basis of cherry coloring of skin or mucus membranes is unreliable. Therefore, only by blood CO determinations or blood oxygen content determinations that we will be able to know that carboxyhemoglobin is the cause of hypoxia in these patients and therefore treat them accordingly. The treatment is directed to improve the alveolar ventilation and increase the alveolar oxygen tension so that by mass action the oxygen will replace the CO on the hemoglobin molecule.[1,2,8,11,12,15] No doubt the vigor of treatment will vary with the extent of carbon monoxide poisoning. There have been good results reported with rapid clearance of CO from the blood in hyperbaric chambers.[16,17]

In smoke poisoning patients who had very high carboxyhemoglobin saturation 82% and 51% with associated clinical interstitial edema, intubation (naso or orotracheal) and use of respirators with PEEP were indicated for both clearance of carbon monoxide and the treatment of hypoxia and interstitial edema. Most of our smoke poisoning patients seemed to rid themselves of CO fairly adequately which may be due to their short exposure time in high concentrations of CO. Their problem, with the exception of one patient, seemed to be injury to respiratory tissue by probably other noxious and irritating gases than the effect of CO per se. The one patient who had carboxyhemoglobin saturation of 82% died 7 hours after admission despite vigorous resuscitation as a result of CNS and myocardial damage. Possibly hyperbaric (2-2½ atmosphere) oxygen chamber may have been of benefit in this case.

The evaluation of late sequelae following inhalation injury was difficult to determine since many of the patients admitted were not seen in the hospital prior to their emergency admission. In the followup clinic visits, six of 40 smoke poisoning patients were felt to have some pulmonary disease such as bronchitis, asthma, and amphysema. Two of five respiratory burn patients similarly demonstrated some mild degree of pulmonary ailment and/or disease. There was one of 40 smoke poisoning patients and three of six carbon monoxide poisoning patients with neurologic sequelae such as residual encephalopathy (poor mentation, choreoathetosis, hemiparesis) and/or peripheral neuropathy. Four of these patients were electively admitted primarily for neurologic evaluation of previous furnace and stove carbon monoxide poisoning.[4]

In spite of controversy in regard to the use of steroids in inhalation injuries, it is our impression that patients with smoke poisoning who sustain peripheral respiratory injury may benefit from 2–4 doses of steroids within the first 24–48 hours, possibly helping to reduce interstitial edema and more significantly to release bronchial and bronchiolar spasm. In respiratory burns, on the other hand, the injury is proximal and central with possible break of respiratory mucosal barrier against invasive infection for which little would be gained by use of steroids and may be harmful since infection plays a major role in such injury. Consequently, in respiratory burns, we have recommended use of penicillin against B-hemolytic streptoccus for the first 3 or 4 days and then the use of proper antibiotics according to culture and sensitivity. Whereas in the case of smoke poisoning since mucosal break is not common initially, the problem is peripheral with bronchospasm, edema, atelectasis and increased secretions. In such cases, therefore, proper antibiotics are only used on the basis of culture and sensitivity in established infections.

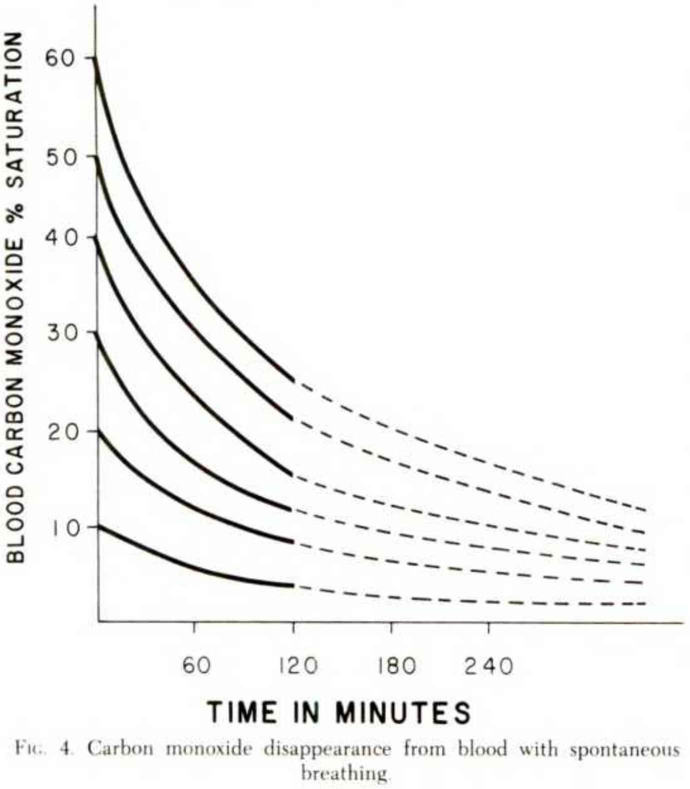

FIG. 4. Carbon monoxide disappearance from blood with spontaneous breathing.

Experimental

In order to learn more as to what smoke poisoning was etiologically as well as pathophysiologically, we had conducted several sets of experiments. In one set we exposed anesthetized mongrel dogs to standardized smokes of wood and kerosene. To our surprise, kerosene smoke neither killed nor produced pulmonary edema whereas wood smoke killed 50–60% of the animals and caused heavy lungs with pulmonary edema and congestion.[20] It was also found that neither carbon monoxide nor soot *per se* caused pulmonary edema or death in animals following resuscitation. Therefore, it was concluded that an invisible noxious gas or gases were responsible for pulmonary damage and death in animals. When wood and kerosene smokes were analyzed by mass spectrometry, gas chromatography and chemical analyses, there were significant quantitative differences in only two gases; carbon monoxide and aldehydes. There was 10 times more carbon monoxide and 15 times more aldehydes in wood smoke than in kerosene smoke. Since carbon monoxide was known and was shown in the above mentioned experiments as non-irritating, aldehydes were considered the likely etiologic gases in the production of exudative pulmonary edema. Short chain aldehydes are well known irritants of mucus membranes in industrial toxicology. In experimental animals these aldehydes have caused pulmonary edema and death. For example, acrolein, a three carbon aldehyde compound in a concentration of 5.5 ppm (parts per million) has been shown to cause irritation of the upper respiratory tract and death with pulmonary edema occurring in a few minutes at a concentration of 10 ppm.[3] In human volunteers, inhalation of acrolein at concentration of 0.805 ppm causes lacrimation and irritation of all exposed mucous membranes.[14] The industrial maximal allowable (MAC) concentration of acrolein is 0.1 ppm.[13] Acrolein was present in wood smoke as 50 ppm and in kerosene smoke as 1 ppm. It is likely that the agents causing tracheo-bronchial and pulmonary parenchymal damage of smoke poisoning in man are also the aldehydes which are found in large quantities in smoke and combustion of wood, cotton, furniture and non-synthetic structural materials.[19]

A mechanism accepted as the basis for the partially irreversible reaction between aldehydes (e.g., formaldehyde) and an amino acid functional group is regarded as being responsible for processes as diverse as tanning leather and producing toxoids for use in vaccines. The inactivation of viruses with formaldehydes, however, is said to be by reaction of the fixative with nucleic acid compound (i.e. RNA in the tobacco mosaic virus) rather than the protein contained in the virus particles.[7] More specifically, the reaction is said to be one of denaturation followed by reaction with freed nucleotide amino groups, especially in the case of adenine and cystosine residues with the reaction most likely occurring with the nitrogen in position 6.[5,6] The denaturation of amino acids or RNA by aldehydes appears to be partial or complete according to the extent of involvement of hydrogen binding sites. It is reasonable to believe that such denaturation by aldehydes is cumulative during long term or repeated exposures. As a result, the possible role of aldehydes in lung damage by cigarette smoking is presently under consideration.

Although our experiments identified carbon monoxide and aldehydes as the poisonous gases from wood, kerosene, cotton and furniture smokes, there is no doubt that other noxious gases such as sulfur or nitrogen oxides, hydrochlorides, hydrocyanic acids, chlorine, fluorine, lead oxides, ammonia and possibly some other gases can damage respiratory tissues when produced in significant concentrations from combustion of other materials.

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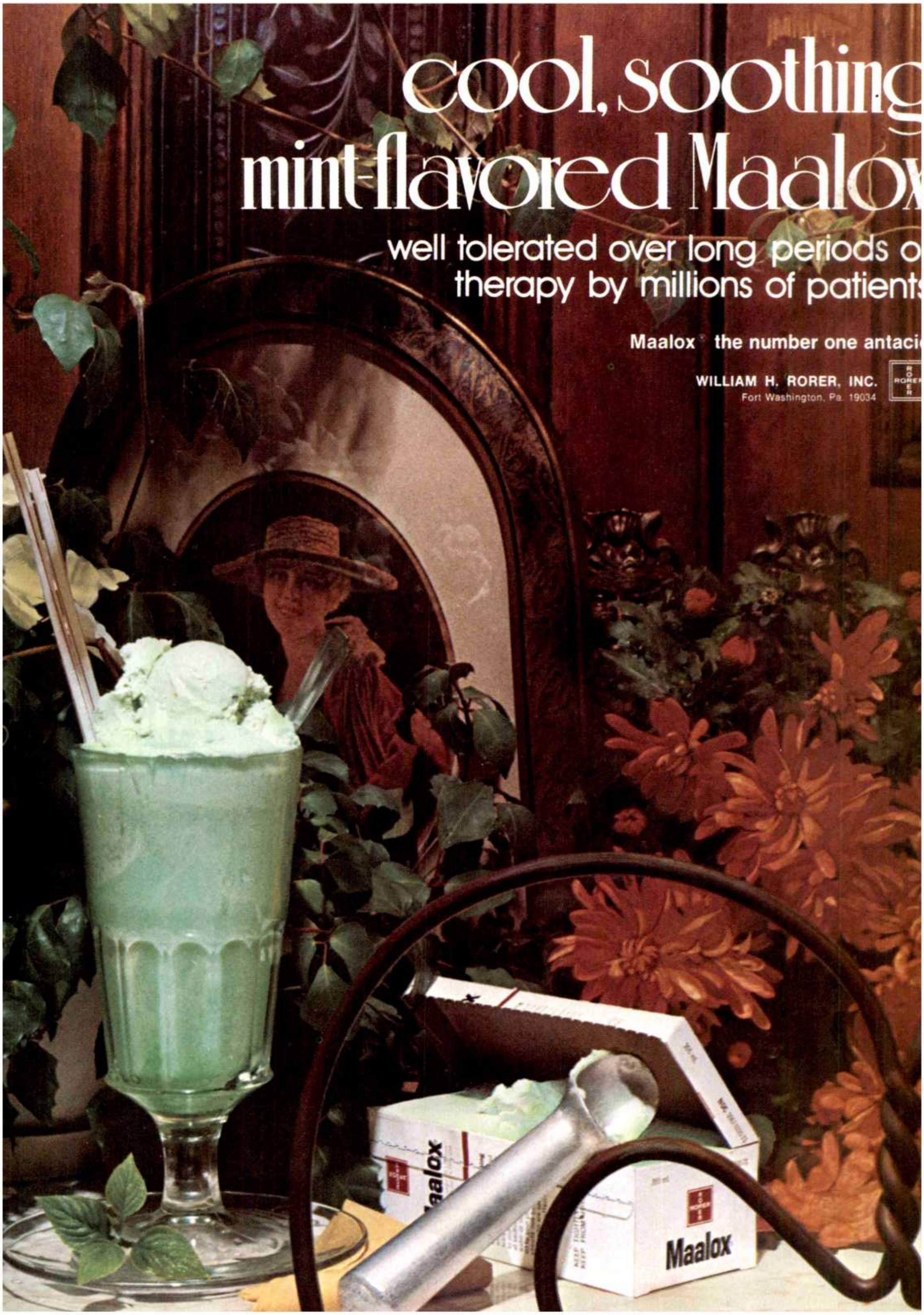
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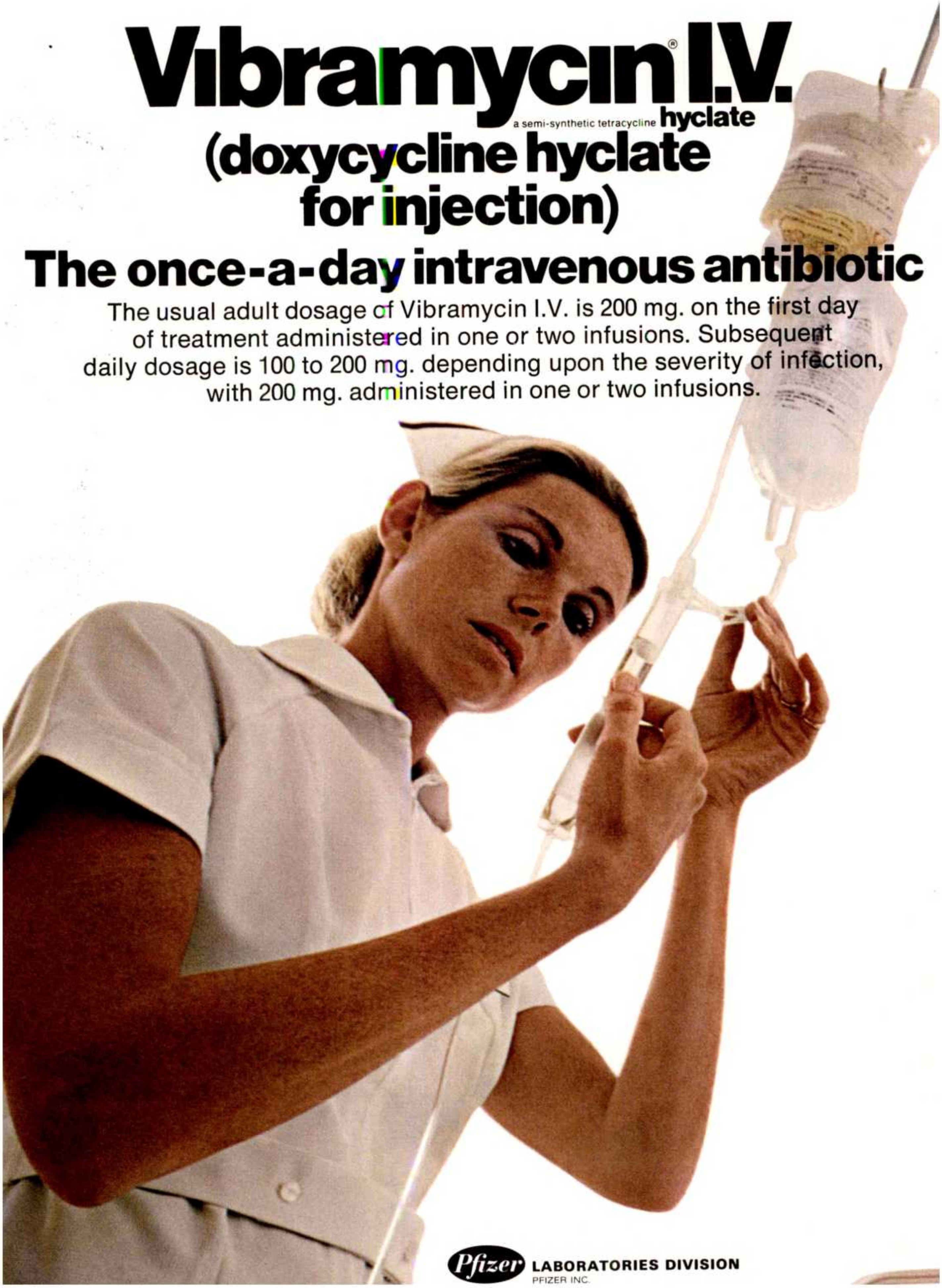

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BRIEF SUMMARY

Contraindicated: In persons hypersensitive to any of the tetracyclines.

Warnings: Use of tetracyclines during the last half of pregnancy, infancy and childhood to the age of 8 years may cause permanent discoloration of developing teeth. This is more common during long-term use of the tetracyclines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. *Thus, tetracyclines should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.* Individuals receiving tetracycline antibiotics should be advised that direct sunlight or ultraviolet light can cause photosensitivity reactions. If these reactions (exaggerated sunburn) occur, discontinue therapy. Doxycycline forms a stable calcium complex in any bone-forming tissue. Fibula growth has been decreased in prematures given oral tetracyclines 25 mg./kg. q. 6 h., but this reaction was reversible when the drug was discontinued.

The antianabolic action of the tetracyclines may cause an increase in BUN. Studies to date indicate that this does not occur to a significant degree with the use of Vibramycin in patients with impaired renal function.

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

Animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus. Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

Precautions: Overgrowth of nonsusceptible organisms may occur, including fungi. If such superinfections are encountered, discontinue Vibramycin and institute appropriate therapy.

In venereal disease when coexistent syphilis is suspected, a darkfield examination should be done before initiating therapy. Conduct monthly serological tests for at least 4 months.

Because tetracyclines depress plasma prothrombin activity, patients on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy, conduct periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic.

Treat all Group A beta-hemolytic streptococcal infections for at least 10 days.

Avoid giving doxycycline with penicillin because of possible interference with penicillin activity.

Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given concomitantly to patients taking oral Vibramycin.

Adverse Reactions: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, maculopapular and erythematous rashes, exfoliative dermatitis, photosensitivity, urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. Prolonged administration of tetracyclines may produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur. Bulging fontanels have been reported in young infants on therapeutic dosage but disappeared when the drug was discontinued. A dose-related rise in BUN has been reported.

Oral Adult and Children's Dosages: See the Vibramycin Oral package insert for recommended dosage schedules for adults and children.

Intravenous Dosage and Administration: *Note:* Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg./day) differs from that of the other tetracyclines (1-2 Gm./day). Exceeding the recommended dosage may result in an increased incidence of side effects.

Studies to date have indicated that Vibramycin, at the usual recommended doses, does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

Intravenous Adult Dosage: The usual dosage of Vibramycin I.V. is 200 mg. on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg. depending on the severity of infection, with 200 mg. administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg. daily for at least 10 days.

Intravenous Children's Dosage: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg./lb. of body weight on the first day of treatment, administered in one or two infusions. Subsequent daily dosage is 1 to 2 mg./lb. of body weight given as one or two infusions, depending on the severity of the infection. For children over 100 pounds the usual adult dose should be used. (See "Warning" Section for Usage in Children.)

General: The duration of infusion may vary with the dose (100 to 200 mg. per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg. of a 0.5 mg./ml. solution is one hour. Desired concentrations of the final solution should be 0.2 mg./ml. to 0.5 mg./ml. Concentrations below 0.1 mg./ml. or above 1.0 mg./ml. are not recommended. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly nor subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

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DEXON in green offers all the advantages of the gold suture... plus the added benefit of high visibility. It is ideal for use in deep tissue or any bloody field—particularly in urologic, intestinal, and gynecologic surgery. Since it leaves no residual color, this green suture may also be used in the skin.

It is available in sizes 1 to 6/0, needled or non-needled, and costs no more than catgut.

Check the visibility of DEXON Green in the fascial closure of an abdominal incision.

DEXON Sutures
Green or Gold

DEXON® polyglycolic acid suture

Complete Product Information

DESCRIPTION DEXON® polyglycolic acid Suture—Synthetic, Absorbable is a homopolymer of glycolic acid. The sutures are sterile, inert, noncollagenous, nonantigenic, nonpyrogenic, flexible, braided, either undyed with a natural beige color or dyed green with D&C Green No. 6. They are uniform in size and tensile strength, but are smaller in diameter than other Absorbable Surgical Sutures of equivalent tensile strength.

ACTIONS When DEXON is placed in tissues a minimal tissue reaction occurs, which is followed by a microscopic layer of fibrous connective tissue which grows into the suture material. Animal studies (subcutaneous tissue in rats, rabbits and dogs) revealed minimal absorption at 7 to 15 days, significant absorption at 30 days, and maximum resorption after 60 to 90 days. Tensile strength, not being a function of the absorption rate, may vary from tissue to tissue, depending in part on the rate of hydrolysis. The early tensile strength of DEXON is reported to be greater than that of comparable chromic catgut. In animal studies (subcutaneous tissue of rats, rabbits and dogs) there occurred a 30 to 50% loss of initial tensile strength in one week and 60 to 80% loss in two weeks, at which time as in the case with chromic catgut no useful residual tensile strength remains.

INDICATIONS DEXON sutures are indicated whenever absorbable sutures and ligatures are employed, provided that extended approximation of tissues is not required or where undue postoperative tension or stress is not anticipated. DEXON is also indicated where non-absorbable sutures are used for their characteristic lack of tissue reaction.

CONTRAINDICATIONS DEXON is contraindicated where extended approximation of tissues under strain must be maintained.

WARNINGS The safe use of this suture in cardiovascular and neural surgery has not been established.

Under certain circumstances, notably orthopedic procedures, immobilization by external support may be employed at the discretion of the surgeon.

Do not resterilize. Discard opened, unused sutures.

PRECAUTIONS Acceptable surgical practice should be followed with respect to drainage and closure of infected wounds. DEXON suture knots must be properly placed to be secure. Therefore, place first throw in precise position for final knot, using a double loop, tie second throw square using horizontal tension; additional throws may be used as desired. Skin sutures which remain in place for periods of longer than seven days may cause localized topical irritation and the extended portion of suture may be snipped off after five to seven days, as indicated.

ADVERSE REACTIONS Those reactions that have been reported include tissue reaction or inflammation, fibrous or granulation tissue, wound separation and bleeding and accumulation of fluid around subcuticular stitches.

DOSAGE AND ADMINISTRATION Use as required. Do not resterilize. Discard opened, unused sutures.

HOW SUPPLIED Suture sizes 7-0 through 2. Supplied in cut lengths or ligating reels, non-needled or affixed to the various DAVIS + GECK ATRAUMATIC® needles in one and three dozen packages.

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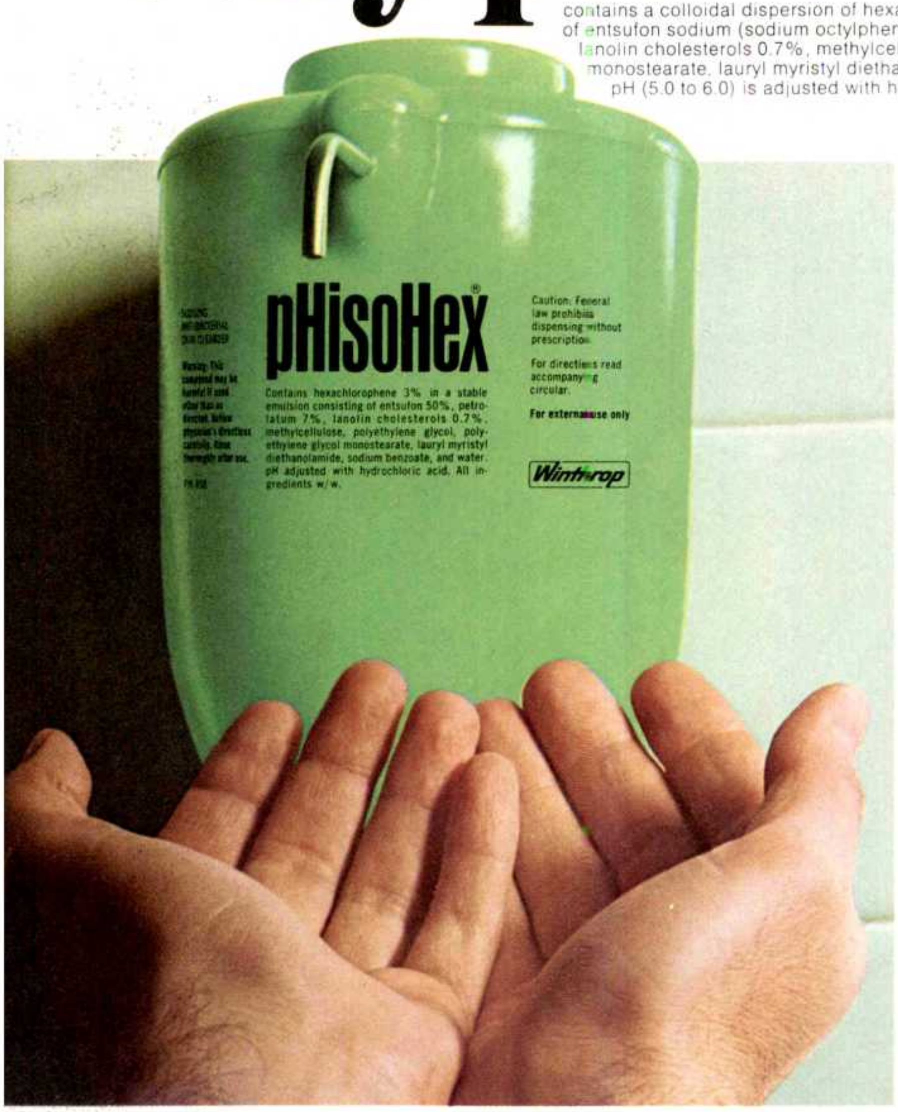
Why pHisoHex®?

contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.


pHisoHex®
Contains hexachlorophene 3% in a stable emulsion consisting of entsufon 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH adjusted with hydrochloric acid. All ingredients w/w.
Caution: Federal law prohibits dispensing without prescription.
For directions read accompanying circular.
For external use only
Winthrop

Why pHisoHex® ?

pHisoHex contains 3% hexachlorophene with cumulative antibacterial action on the hands, unique among antibacterial agents.

Why is this important?

pHisoHex continues to protect during the interim between scrubs if used regularly as directed.

Is there an alternative?

While more frequent washing with other agents is an alternative, it is not a practical one for prolonged surgery.

But there's no need for an alternative!

Nonalkaline, hypoallergenic pHisoHex is clearly indicated for staphylococci and other gram-positive bacteria as a bacteriostatic hand cleanser and surgical scrub. *Rinse thoroughly after use.*

pHisoHex®

sudsing antibacterial soapless skin cleanser

pHisoHex contains a colloidal dispersion of hexachlorophene 3% in a stable emulsion consisting of entsufon sodium (sodium octylphenoxyethoxyethyl ether sulfonate) 50%, petrolatum 7%, lanolin cholesterols 0.7%, methylcellulose, polyethylene glycol, polyethylene glycol monostearate, lauryl myristyl diethanolamide, sodium benzoate, and water. pH (5.0 to 6.0) is adjusted with hydrochloric acid. All ingredients w/w.

Actions: pHisoHex has bacteriostatic action against staphylococci and other gram-positive bacteria. Cumulative antibacterial action develops with repeated use.

Indications: pHisoHex is indicated for use as a surgical scrub and a bacteriostatic skin cleanser. It may also be used for washing to control an outbreak of gram-positive infection in the nursery when good hospital practice has been inadequate as a total program of infection control. It should be used only as long as necessary for infection control. (See Warnings.)

Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

PHISOHEX SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

Winthrop

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New York, N.Y. 10016

(16264)

Schering

In serious gram-negative infections*

Three good reasons to initiate therapy with Garamycin® Injectable

(gentamicin sulfate)

1. Unique spectrum.

2. Incidence of bacterial resistance is low and has not increased significantly.

3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

*Due to susceptible organisms

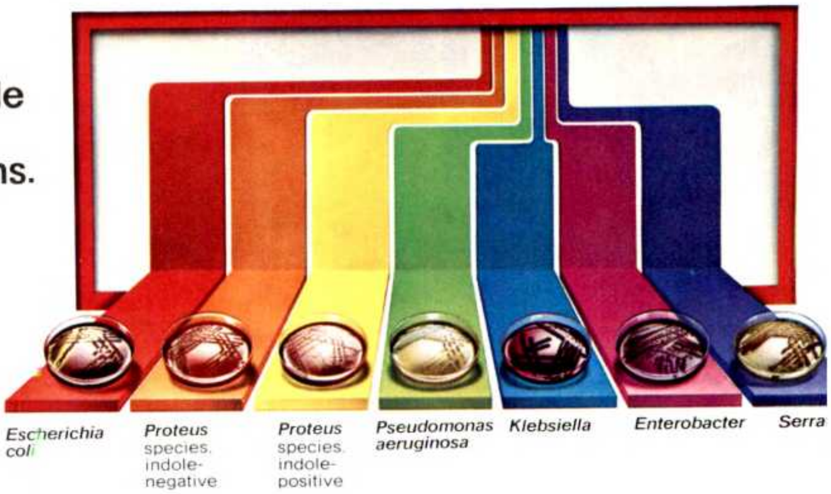
1. Unique spectrum.

Garamycin Injectable (gentamicin sulfate) is active against susceptible strains of seven major gram-negative pathogens.

These are:

Escherichia coli
Proteus, indole-negative
Proteus, indole-positive
Pseudomonas aeruginosa
Klebsiella } species
Enterobacter } species
Serratia } species

Garamycin Injectable is also highly effective against susceptible strains of **Staphylococcus aureus** and may be considered when penicillins are contraindicated.



2. Incidence of bacterial resistance is low and has not increased significantl

*In vitro** susceptibility virtually unchanged

* *In vitro* susceptibility data are not necessarily indicative of clinical effectiveness.

In a five-year study[1] in over 100 hospitals, gram-negative pathogens identified and tested demonstrated high susceptibility to GARAMYCIN. From 1970 through 1974, there was virtually no change in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

In the seven or eight years' experience of one investigator[2] where gentamicin has been restricted to parenteral use, resistance has not appreciably changed.

Resistance has been demonstrated to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported.

References

1. I.M.S. Audit of Pathology Cultures—1970-74.
2. Jackson, G.G.: Highlights of a Symposium on Gentamicin, a filmed panel discussion summarizing a symposium on gentamicin, University of California School of Medicine, Los Angeles, January 26, 1971.

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Schering

3. Relatively low order of adverse renal and eighth nerve reactions when used as directed.

Adverse renal reactions

The risk of adverse renal reactions is low in patients with normal renal function. Usually manifested by nitrogen retention as evidenced by a rising BUN and creatinine, they occur most often in patients with pre-existing renal damage and in patients receiving larger than recommended doses or treated for longer periods of time than recommended. See Warning Box below.

Adverse eighth nerve reactions

The incidence of adverse eighth nerve reactions with GARAMYCIN Injectable is relatively low. When occurring, the effect is predominantly on the vestibular branch of the eighth cranial nerve, resulting in vestibular dysfunction with vertigo and tinnitus. These symptoms have, in many cases, been transitory. The known effect on the auditory branch to date mostly has involved only the high-frequency hearing ranges. See Warning Box below.

A logical choice

in serious gram-negative infections⁺

pneumonia
urinary tract infections
septicemia
wound infections

⁺Due to susceptible organisms

Garamycin®
gentamicin sulfate
injectable
40 mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

See Clinical Considerations section which follows...

Schering

A logical choice
in serious gram-negative infections*

GARAMYCIN® Injectable, brand of gentamicin sulfate, U.S.P., injection, 40 mg. per ml. Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin
For Parenteral Administration

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

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Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents, such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommende for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., is supplied in 2 ml. (80 mg.) multiple-dose vials and in 1.5 ml. (60 mg.) and 2 ml. (80 mg.) disposable syringes for parenteral administration.

Also available, GARAMYCIN Pediatric Injectable, 10 mg. per ml., supplied in 2 ml. (20 mg.) multiple-dose vials for parenteral administration.

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For more complete prescribing details, consult Package Insert or Physicians' Desk Reference. Schering literature is also available from your Schering Representative or Professional Services Department, Schering Corporation, Kenilworth, New Jersey 07033.

Garamycin®
gentamicin sulfate
Injectable
40 mg./ml.

Each ml. contains gentamicin sulfate equivalent to 40 mg. gentamicin

*Due to susceptible organisms

SLS-0

Characterization of Elevated Fibrin Split Products Following Thermal Injury

P. WILLIAM CURRERI, M.D.,* MARY E. WILTERDINK, B.S., M.T., (ASCP), CHARLES R. BAXTER, M.D.

From the Department of Surgery,
The University of Texas Southwestern
Medical School, Dallas, Texas

These studies establish that the staphylococcal clumping test is superior to the tanned red cell hemagglutination inhibition immunoassay for monitoring fibrin split product concentration in burn sera. It is strongly suggested that the principal circulating degradation product is a complex of soluble fibrin monomer with fragment D. Finally, there does not appear to be any effect on measured fibrin split product concentration in sera of burn patients receiving prophylactic heparin or aspirin.

ELEVATED LEVELS of fibrin split products (FSP) have been reported to occur frequently in both thermally injured patients and experimental burns. Both the staphylococcal clumping test (SCT) and the tanned red cell hemagglutination inhibition immunoassay (TRCHII) or Merskey method have been advocated for screening burn patients with suspected intravascular coagulation. The Merskey method has been utilized to detect the presence of X, Y, and D fragments in defibrinated plasma. It is only slightly reactive with fragment E. The staphylococcal clumping test is positive in the presence of X and Y fragments, as well as soluble fibrin monomer or polymer complexes with fragments Y and D. In this study these two assays were used to analyze the plasma fibrin split product concentration in burned patients during the first two post-burn weeks.

Methods

Blood samples for the tanned red cell hemagglutination inhibition immunoassay were collected in vacutainer tubes containing 3.8% sodium citrate (1 : 10 volume) and Trasylol (25 Christensen units of antiplasmin/ml). Samples were centrifuged, the plasma treated with thrombin, and the serum immediately frozen for future testing. The fibrin split products level of each serum sample were determined according to the method of Merskey *et al.*,[4] which depends on the neutralization of antihuman fibrinogen antiserum by fibrinogen or fibrin degradation products. Neutralized antiserum blocks the agglutination of tanned sheep red blood cells coated with human fibrinogen. Thus, the titer of fibrin split products is the highest dilution of test serum which clearly inhibits red cell agglutination by the antiserum. The use of known standards allows quantitation of fibrin split product concentration and normal values range from 2 to 5 μg/ml.

The blood samples for the staphylococcal clumping test were drawn into tubes containing soybean trypsin inhibitor (0.5 mg antiplasmin/ml blood) and thrombin (100 units/ml blood). The tubes were mixed well and incubated at 37 C until clot retraction was evident, approximately two hours. Serum was then obtained by centrifugation and samples frozen for future testing. The test was performed on microtiter plates as described by Leavelle and associates.[2] The presence of a clumping factor (bound coagulase) on the cell walls of certain strains of Staphylococcus aureus produces visible clumping of the bacteria in the presence of fibrinogen, some early high molecular weight breakdown products, and soluble fibrin monomer complexes. Simultaneous determinations of known standards prepared from normal plasma allow the quantitation of the fibrin split product concentration. The mean value obtained from an uninjured control population was 2.7 ± 2.1μg/ml.

A prospective patient study was subsequently instituted

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* Recipient of Research Career Development Award from the National Institutes of Health.

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to test the effectiveness of prophylactic systemic anticoagulation in preventing abnormal elevations of fibrin split product concentration in the immediate post burn period. Thirty-one patients with greater than 30% total body surface burns, who had no gross contraindications for systemic anticoagulation, were randomly assigned to one of three patient groups. One group was administered Heparin, 5,000 units (subcutaneously) every six hours during the first two post-burn weeks. A second group received aspirin, 10 grains per rectum, during the same time period. A control group of patients received neither heparin nor aspirin. Blood samples for the staphylococcal clumping test were drawn at least once every three days and the results grouped arbitrarily into three day periods.

Results

Serum from 55 burned patients was simultaneously assayed serially during the first two post-burn weeks for fibrin split products by both the tanned red cell hemagglutination inhibition immunoassay and the staphylococcal clumping test. Values obtained by the Merskey method were normal on all occasions in 23% of patients (mean = 2.90μg/ml), minimally elevated in 49% (mean = 7.20μg/ml) and significantly increased in 27% (mean = 16.33μg/ml) (Table 1). Fibrin split product concentration measured by the staphylococcal clumping test were increased above normal in all patients at some period during the first two post-burn weeks. Only 7% had minimal elevation (mean = 6.77 ± 0.07μg/ml), and 93% had at least four times maximum normal concentration (mean = 41.33 ± 4.7μg/ml). Fibrin split products observed by the staphylococcal clumping test were consistently elevated between the fourth and eighth post-burn day, and although the levels of fibrin split products were somewhat more variable after this time, the concentration remained greater than accepted normal concentration throughout the study period (Fig. 1).

No significant differences in fibrin split product concentration were noted in the patients who received prophylactic heparin or aspirin when compared to those patients receiving no anticoagulant therapy (Fig. 2). Serum from all three groups contained markedly elevated levels of fibrin split products as measured by the staphylococcal clumpin test.

TABLE 1. *Fibrin Split Product Concentration in Sera from Burn Patients as Measured by the TRCHII and SCT Methods*

	Range μg/ml	Number of Patients	Per Cent of Total	Mean ± S.E.
TRCHII	<3.6	13	23	2.9 ± 0.38
(Normal =	3.6–7.2	27	49	7.2 ± 0
2–5 μg/ml)	>7.2	15	27	16.3 ± 1.31
SCT	0–3.4	0	0	
(Normal =	3.4–6.7	4	7	6.7 ± 0.07
(2.7 ± 2.1 μg/ ml)	>6.7	51	93	41.3 ± 4.74

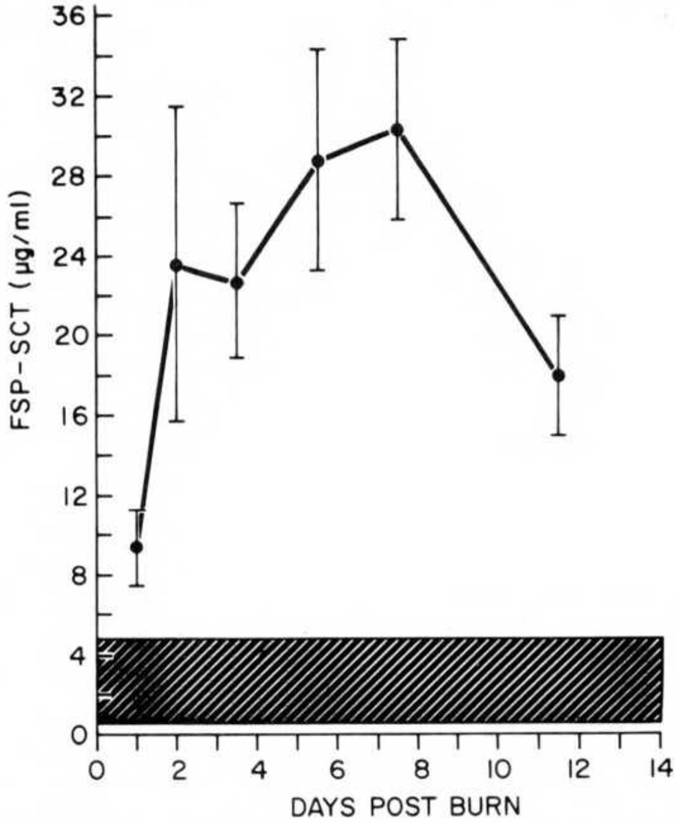

FIG. 1. Fibrin split product concentration in sera from burn patient measured by the staphylococcal clumping test during the first two post burn weeks.

Discussion

Interpretation of these results required knowledge of th normal degradation pathway of fibrinogen and fibrin b plasmin. In addition, the specificity of both the tanned re cell hemagglutination inhibition immunoassay and th staphylococcal clumping test in detecting each degradatio product must be appreciated.

The scheme of the degradation of fibrinogen and fibrin b plasmin is shown in Fig. 3. The initial digestion results i the conversion of fibrinogen (MW 340,000) to Fragment (MW 270,000) plus small polypeptide fragments. X undergoes further proteolysis and is degraded to Fragment (MW 165,000) and Fragment D (MW 85,000). Y is spli further, yielding Fragments D and E (MW 55,000) whic are immune to further digestion by plasmin. The net resul of the degradation of one mole of fibrinogen by plasmin is moles of D and an E fragment. During this proteolysis fragments X, Y, and D also may complex with fibri monomers, resulting in non-clottable soluble fibri monomer complexes (SFMC).

Trasylol and soybean trypsin inhibitor are added to th

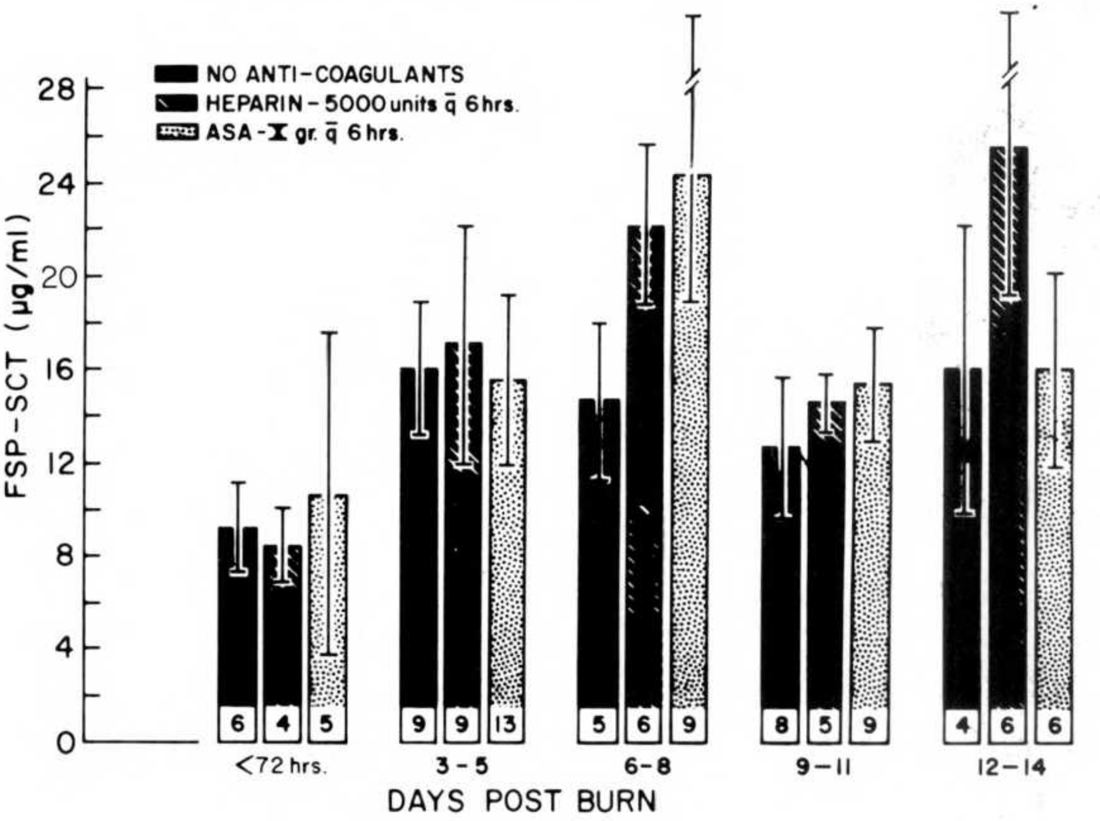

FIG. 2 Comparison of fibrin split product concentration in sera from burn patients receiving various prophylactic anticoagulant regimens.

samples to inhibit *in vitro* the fibrinolytic activity of plasmin. The addition of thrombin in both tests, as well as the two hour incubation period in the staphylococcal clumping test, are necessary to insure the complete conversion of fibrinogen to fibrin, and its removal in the clot. Consequently, the test serum will contain only *non-clottable* fibrin or fibrinogen split products, plus soluble fibrin monomer complexes that were present in the patient's blood at the time of phlebotomy.

The extensive studies of Marder and associates[3] have elucidated the reactivity and sensitivity of the tanned red cell hemagglutination inhibition immunoassay and the staphylococcal clumping test with plasmin digests of purified human fibrinogen, fibrin, purified degradation products, and with serum obtained from patients suspected of having circulating degradation products. These investigators have shown that the Merskey method is strongly reactive with undigested fibrinogen, fragments X, Y, and D, and slightly reactive with E. The staphylococcal clumping test is less sensitive than the tanned red cell hemagglutination inhibition immunoassay and its reactivity progressively decreases with each stage of fibrinogen digestion; it does not react at all with fragments D and E. In fact, the staphylococcal clumping test detects only fibrinogen, X, Y, and soluble fibrin monomer complexes.

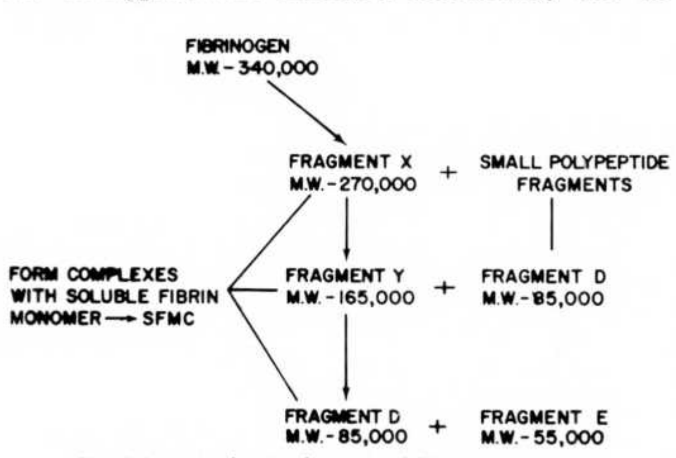

FIG. 3 *In vitro* plasmin digestion of fibrinogen and fibrin.

Therefore, the serum isolated from burned patients in this study can be qualitatively analyzed by examination of the possible fibrin degradation products which might still be present following thrombin precipitation and would also be detectable by either or both assays for fibrin split products. Elevated values of fibrin split products by the Merskey test would be detected only in the presence of increased levels of fragments Y, D, or E. On the other hand, increased fibrin split product levels by the staphylococcal clumping test should only be seen with elevated concentrations of fragment Y or soluble fibrin monomer complexes with fragments X, Y, or D.

Previous studies[1] in our laboratory have shown that all fibrin split products detected by the staphylococcal clumping test disappear with the addition of protamine sulfate. Protamine sulfate is very effective in disassociating soluble fibrin monomer complexes and removing the monomer by gelation or paracoagulation.[5] Since the staphylococcal clumping test will detect both free X and free Y fragments following disassociation by protamine sulfate, complexes of these fragments with soluble fibrin monomer are unlikely. Therefore, most of the measured fibrin split products in burn sera must be composed of fragment D and complexes of fragment D with soluble fibrin monomer. Verification of these analyses by purification of fibrin split products utilizing column chromatography and gel electrophoresis is currently being pursued in our laboratory.

It appears that complexes between fragment D and soluble fibrin monomer are more commonly present in burn sera, since the staphylococcal clumping test was so much more sensitive in this series of patients. This finding is at variance with the observations of Marder and his associates[3] in sera obtained from *unburned* patients suspected of intravascular coagulation. They not only noted a slightly greater sensitivity of the Merskey method in detecting fibrin split products in their patient population, but also observed a decrease in fibrin split product concentration coincident with heparin anticoagulation.

Failure to alter fibrin split product concentration in randomly assigned burned patient populations receiving heparin therapy was somewhat surprising. It is, of course, possible that inadequate anticoagulation was achieved although most patients exhibited simultaneous prolongation of their partial thromboplastin time. More likely, the elevated fibrin split product elevation seen in the post-burn period is not secondary to abnormal intravascular coagulation but rather secondary to coagulation in the extracellular edema fluid. Such extravascular plasmin activity would respond to heparin more slowly and might require extremely high doses, which may be clinically unacceptable. The unique predominance of soluble fibrin monomer complexes in the burned patient may also be related to the unusual extravascular site of fibrinogen and fibrin degradation.

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Coagulation Dynamics Following Thermal Injury:

Effect of Heparin and Protamine Sulfate

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A burned rat model was developed to examine post-burn alterations in coagulation. Fibrin split product concentration, as measured by the staphylococcal clumping test, was noted to rise significantly within the first 24 hours following injury. Prophylactic *in vivo* systemic anticoagulation with heparin was ineffective in modifying this response. However, systemic administration of protamine sulfate prevented post-burn elevation of fibrin split products. *In vitro* fibrin split product concentration in burn sera following the addition of heparin and protamine sulfate, was also analyzed. The results of these experiments elucidated the biochemical effects of protamine sulfate on circulating fibrin degradation products in the rat burn model.

PREVIOUS REPORTS by both Baxter[2] and McManus[9] have noted the presence of an increased concentration of fibrin split products in plasma of seriously burned patients during the first post-burn week. Presumably such increases in fibrin split product concentration result from activation of plasmin in response to significant intravascular or extravascular coagulation.

In this study, a rat burn model was utilized to describe alterations in the coagulation mechanism with time. Since the animals all received standardized scald burns, carefully controlled post-burn therapy with systemically administered anticoagulants could be evaluated.

Methods

One-hundred five, 200 gm male Sprague-Dawley rats were subjected to scalding water at 98 C for 10 seconds to effect either a 30% or 50% full-thickness burn utilizing the method of Walker and his associates.[15] All animals were resuscitated with two 10 ml intraperitoneal injections of lactated Ringer's solution; one dose delivered immediately post-burn and a second given one hour later. Blood samples were obtained by cannulation of the abdominal aorta. After separation of either plasma or serum, samples were frozen for later laboratory analysis.

Fibrinogen determinations were performed according to the method of Ratnoff.[11] Platelet counts were performed on a Coulter Counter. Prothrombin time, partial thromboplastin time, and thrombin times were obtained by standard laboratory techniques. The staphylococcal clumping test as modified by Leavelle[7] was utilized to assay fibrin split product concentration.

Serum samples from 105 burned rats and 55 burned patients were subjected to quantitative analysis for fibrin split product concentration. Additional thrombin (100 units/ml serum) was then added to remove any remaining fibrinogen or large molecular weight X fragments and the fibrin split product assay repeated. The supernatant was then treated with protamine sulfate (10 mg/ml serum) and incubated for 20 minutes at 4 C to disassociate soluble fibrin monomer complexes. The fibrin monomers then undergo gelation or paracoagulation allowing their removal by centrifugation. The supernatant now containing only Y, D, or E fragments was again assayed by the staphylococcal clumping test.

A 30% burned rat model was utilized to evaluate the effect of systemic heparin or protamine sulfate on the post-burn appearance of elevated fibrin split product levels. Therapeutic doses of heparin (10 units/100 gm body weight) or protamine (0.1 mg/100 gm body weight) were injected subcutaneously immediately prior to burning and then every four hours until sacrifice at 24 hours. Separate groups of unburned rats and burned rats received sub-

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cutaneous injections of 0.2 ml physiological saline at the same time intervals and served as controls.

Results

Alterations in coagulation parameters with time in the rat burn model are summarized in Fig. 1. Fibrinogen concentration increased from 194 ± 22.3 mg% in the unburned rat to a peak of 691 ± 13.7 mg% two days post-burn ($p < .001$). Fibrin split products increased from 2.7 ± 0.59 μg/ml to 13.0 ± 2.65 μg/ml at day one post-burn ($p < .01$). No significant prolongation of thrombin time, partial thromboplastin time, or prothrombin time was observed. In fact, a state of hypercoagulability was suggested. Platelet concentration was normal during the early post-burn period.

In vitro addition of thrombin to burned rat or human serum did not result in any further clotting, and did not reduce the measured concentration of fibrin split products. However, the addition of protamine sulfate resulted in the loss of all fibrin split products measured by the staphylococcal clumping test, suggesting the presence of complexes between D fragments and soluble fibrin (Table 1).

In vivo protamine sulfate therapy pre- and post-burn was instituted to determine if the subsequent elevation of circulating fibrin split products at 24 hours could be prevented. In the 30% rat model, burned rats receiving systemic protamine sulfate had normal fibrin split product levels at 24 hours post-burn in contrast to rats receiving physiologic saline solution or heparin, which exhibited elevated serum concentrations of fibrin split products as measured by the staphylococcal clumping test (Table 2).

Discussion

In this study we were able to utilize a highly reproducible animal burn model for evaluation of alterations in the coagulability of blood following controlled burn injury. Alterations in clotting factors with time were strikingly similar to those observed in the burned patient as previously reported by Curreri[3] and Baxter.[2]

To our knowledge, characterization of the fibrin split products, measured by the staphylococcal clumping assay in burned patients, has not previously been attempted. The staphylococcal clumping assay is known to detect fibrinogen, X and Y fragments, and complexes of X, Y, and D fragments with soluble fibrin monomers.[8] The results of this study strongly suggest that the major fibrin split product measured by the staphylococcal clumping test in both burned animals and burned patients during the early post-burn period is a complex between D fragments and soluble fibrin monomer. When excess thrombin is added to serum, all remaining fibrinogen and X fragments are removed. Precipitates during this step were not observed and no decrease in fibrin split product levels was observed in the supernatant. Thus X fragments cannot account for any substantial portion of the measured fibrin split products. Niewiarowski[10] has shown that protamine sulfate disassociates soluble fibrin monomer complexes, releasing free fibrinogen degradation fragments and precipitating polymerized soluble fibrin monomer. In this experiment the addition of protamine sulfate was associated with the disappearance of fibrin split products as measured by the staphylococcal clumping test. A complex of soluble fibrin

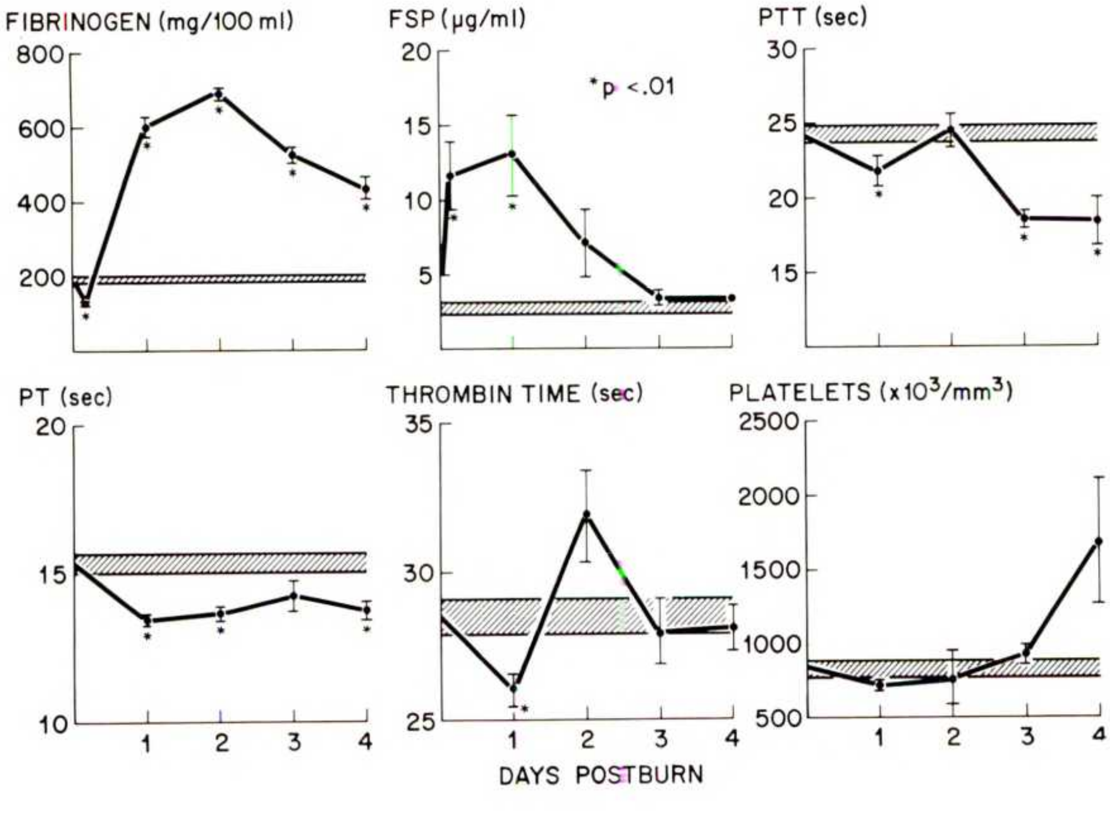

FIG. 1. Alteration of coagulation parameters with time in the rat burn model. Note early significant rise in fibrinogen and fibrin split product concentration.

TABLE 1. *Effect of Thrombin and Protamine Sulfate on In Vitro Fibrin Split Products*

	Serum	+ Thrombin	+ Protamine Sulfate
Human	21.7 ± 2.43	20.84 ± 2.30	0
Rat	9.45 ± 2.10	10.05 ± 1.63	0

monomer with Y fragments would yield free Y fragments in the presence of protamine sulfate. Since Y fragments will be detected by the staphylococcal clumping test, one must conclude that the soluble fibrin monomer complexes in the burned patient or animal are primarily D fragment complexes.

Further corroboration of these conclusions was noted in the *in vivo* studies where it was found that protamine sulfate administration prevented the elevation of fibrin split products in serum from burned animals. Since heparin had no effect on post-burn fibrin split product levels, the observation in animals receiving protamine sulfate was not simply due to the anticoagulant properties of the drug. In fact, since heparin anticoagulation prior to burning failed to prevent the rise in fibrin split products, it appeared that the source of the fibrin split products is more likely to be extravascular rather than intravascular.

The toxicology of purified fibrin split products has not yet been elucidated. The appearance of elevated post-burn levels of fibrin split products, as measured by the staphylococcal clumping test, can be circumvented by systemic administration of protamine sulfate. However, in all likelihood the net effect of protamine sulfate is to substitute circulating free, low molecular weight D fragments for D fragment-soluble fibrin monomer complexes of high molecular weight. Whether this offers any pharmacologic or toxicologic advantage remains unknown. Clinical and autopsy examination revealed no significant differences at 24 hours post-burn in rats whether treated with systemic saline, heparin or protamine sulfate.

The administration of systemic heparin anticoagulation in the treatment of burns has been independently advocated recently by Saliba,[12-14] Johansson,[5,6] Arturson,[1] and Elrod.[4] Improved survival, preservation of platelet and fibrinogen concentrations, diminished pain, decreased edema, reduction in resuscitative fluid requirements, and more rapid wound healing have all been associated with systemic anti-coagulation of the burned animal or patient with heparin. Many of these therapeutic claims have been concluded from data derived from uncontrolled experimental protocols. We were unable to show any effect on fibrin split product concentration in animals treated with heparin prior to and following burn injury in this study. Thus, the beneficial effect of heparin, if any, in the treatment of burned patients would appear more likely to be associated with pharmacologic actions of the drug other than anti-coagulation. Since complications associated with anti-coagulation in the burned patient may be formidable as well as life-threatening, we would not advocate its prophylactic use at the present time.

TABLE 2. *In Vivo Heparin and Protamine Sulfate Therapy—Rat Study*

	Non Burn	Burn (30% TBSA)	Heparin	Protamine Sulfate
Number	5	5	5	5
Subcutaneous Injection Every 4 Hours	N.S.—0.2 ml	N.S.—0.2 ml	Heparin 20 units	Protamine Sulfate 0.2 mg
FSP-SCT 24 Hours Post Burn	2.38 ± 0.93	14.74 ± 7.34	18.76 ± 7.34	3.40 ± 0.0

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Villous Tumors of the Duodenum

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Villous tumors of the duodenum are rare, but treatment may be problematic because of their association with invasive adenocarcinoma. Two cases of villous tumor of the duodenum are described and 39 other reported cases are reviewed. Presenting symptoms were bleeding 27%; obstruction 24%; jaundice 22% and vague dyspepsia 20%. Diagnosis may be made by radiographic barium contrast evaluation of the duodenum, especially with the addition of air contrast hypotonic studies and by fibro-optic endoscopy. Twenty-seven per cent of villous tumors of the duodenum are associated with adenocarcinoma. Invasive tumor is more common in patients over 50 years old (35%), in tumors of the third and fourth portions of the duodenum (44%) and in tumors over 4 cm in diameter (30%). Local excision is the treatment of choice for benign lesions. Pancreatico-duodenectomy is recommended for tumors which include invasive carcinoma in patients without distal metastases.

ALTHOUGH fewer than 200 cases of epithelial tumors of the duodenum have been reported, recent advances in radiographic and endoscopic diagnostic techniques have led to the earlier and more frequent recognition of these lesions (Fig. 1). They include benign adenomatous polyp, Brunner's gland adenoma, villous tumor, and frank invasive adenocarcinoma. Benign tumors are adequately treated by local excision. Pancreatico-duodenectomy is usually recommended for invasive adenocarcinoma. Most villous tumors are benign, but since areas of frank invasion are frequently observed, the appropriate choice of treatment may be difficult. The present report reviews 39 cases of villous tumor of the duodenum described in the world literature and describes two new cases, with special emphasis on the choice of surgical treatment.

Case Reports

Case 1: J.F., a 52-year-old white woman, was admitted to New York University Hospital on January 7, 1973. She complained of vague dyspepsia for a six-year period and of increasing eructation during the five months prior to admission. There had been no melena, hematemesis, vomiting or abdominal pain. Radiographic barium contrast evaluation of the duodenum prior to admission had revealed a smooth filling defect in the second portion of the duodenum. Physical examination was normal. Laboratory data was: hematocrit 36%, white blood cell count 5,900/cu mm, total serum bilirubin 0.3 mg% and alkaline phosphatase 75 mU/ml (normal 30–100).

Celiac angiography performed on January 8, 1973, showed medial displacement of the gastroduodenal artery, with a few irregular vessels noted arising from the retroduodenal portion of that artery. Hypotonic air contrast barium study of the duodenum on January 9, 1973, showed a smooth mass in the second portion of the duodenum adjacent to the ampulla of Vater. Surgical exploration on January 11, 1973 revealed a sessile polypoid tumor, which was generally soft but had several firm areas. Frozen section examination showed villous adenoma with possible invasion. Pancreatico-duodenectomy was performed. The postoperative course was uneventful and the patient was discharged home on January 25, 1973. She has remained well during her one-year followup.

Pathological examination of the operative specimen showed a 4 × 0.7 × 4 cm sessile villous adenoma. The tumor was on the medial wall of the duodenum, 7 cm from the pylorus, but did not involve the ampulla of Vater. There was no evidence of carcinoma on the final sections (Fig. 2).

Case 2: D.G., a 69-year-old white woman, was admitted to New York University Hospital on September 5, 1973. For five years she had experienced epigastric distress, which had been attributed to a hiatal hernia. Barium contrast radiographic evaluation of the upper gastrointestinal tract two years prior to admission demonstrated a large hiatal hernia and a pedunculated lesion of the first portion of the duodenum. A repeat study, three months prior to admission, showed an increase in the size of the duodenal lesion. There were no other gastrointestinal symptoms.

Physical examination was normal. Laboratory data included: hematocrit 37%, white blood cell count 4,500/cu mm, total serum bilirubin 0.6 mg% and alkaline phosphatase 46 mU/ml (normal 30–100).

Laparotomy on September 3, 1973 revealed a 3 cm pedunculated polyp in the first portion of the duodenum and a 15 × 6 cm hiatus hernia sac. The hiatus hernia was repaired and an anterior duodenotomy was then made. The duodenal polyp had a stalk 2 cm in length. The base of the stalk was divided and oversewn and the duodenotomy was closed. The postoperative course was smooth and the patient was discharged on September 21, 1973.

Pathological examination of the specimen showed a mixed epithelial

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polyp 3 × 2 × 1.5 cm in size, with villous and adenomatous elements. The stalk was free of villous elements. No carcinoma was noted (Fig. 3).

Discussion

Neoplastic growth in the small intestine is relatively infrequent. Its incidence is one-tenth that of similar lesions of the colon.[39,50] Furthermore, lesions of the small intestine are frequently benign[39] and asymptomatic, and may therefore be recognized only as incidental findings at autopsy.[41] Although the duodenum comprises 8% of the small bowel by length, it harbors 10–22% of small intestinal tumors.[3,19].

Forty-eight per cent of all duodenal tumors are benign.[3,8,10,12,15,19,21,24,25,28,39,45,47] They include adenomas (45%), lipomas (18%), myomas (16%), fibromas (10%), angiomas (4%), neurogenic lesions (3%) and less common lesions including polyposes, teratomas and villous tumors.[41]

The remaining 52% of duodenal tumors are malignant. They include adenocarcinomas (87%) and sarcomas (13%).[26] Carcinoid tumors and lymphomas are also found in the duodenum.[19] Approximately 45% of all small bowel carcinomas occur in the duodenum.[22]

One per cent of duodenal tumors are villous in nature. The villous tumor is an epithelial lesion[27] arising from or migrating on the surface of the mucus membrane.[43] The term "villous" tumor arises from the fact that these lesions have a velvety texture with finger-like projections resembling villi. It has also been called papilloma, papillomatous polyp, papillary tumor, papillary adenoma, papillary polyposis, villous papilloma and villous adenoma.[43] On microscopic examination it has frond-like projections of mucosa with branching papillary structure[23] (Figs. 2 and 3).

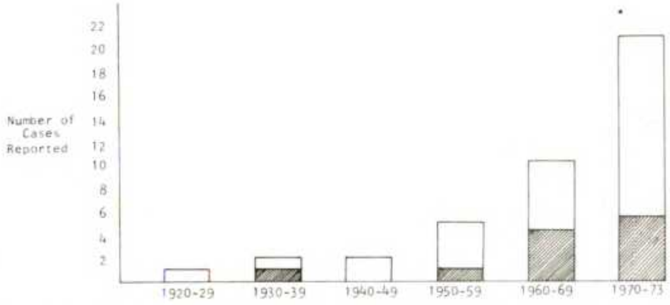


FIG. 1. Number of cases of duodenal villous tumor reported in each decade since 1920. The cross-hatched areas represent villous tumors with invasive carcinoma.

Villous tumors are seen most frequently in the colon where they comprise 5–28% of all benign tumors.[17,23,36] Up to 88% of colonic villous tumors are in the distal sigmoid and rectum.[35] The reported incidence of invasive adenocarcinoma in villous tumors of the colon and rectum is 30%[2,35,43] with a range of 5%[23] to 55%.[17] Because of the frequent malignant associations of villous tumors, total excision biopsy is usually recommended.[2,4]

In the rectum, as in the duodenum, complete excision of the involved bowel results in major morbidity and assessment of the presence or absence of invasive carcinoma in villous tumors assumes increased importance.

A total of 82 villous tumors of the stomach have been reported.[6,49] Gastric polyps are found in 0.2% of autopsies[16]

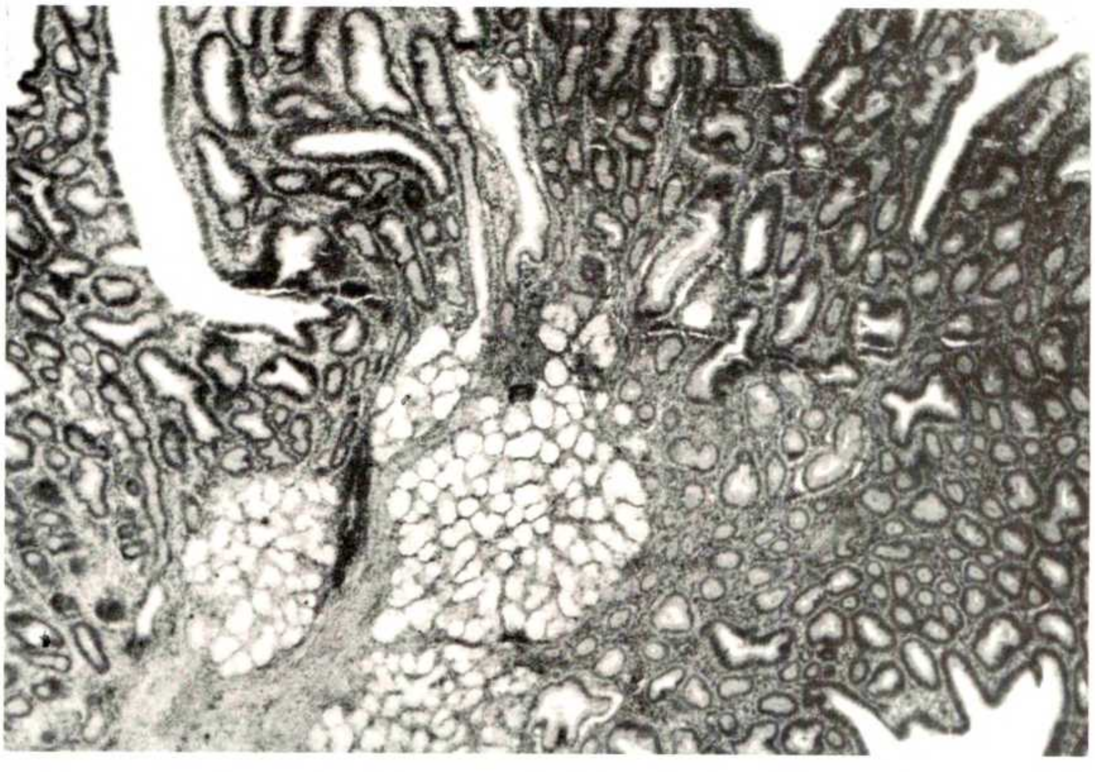


FIG. 2. Photomicrograph of tumor from Case One. (Hematoxylin and Eosin × 100 original magnification)

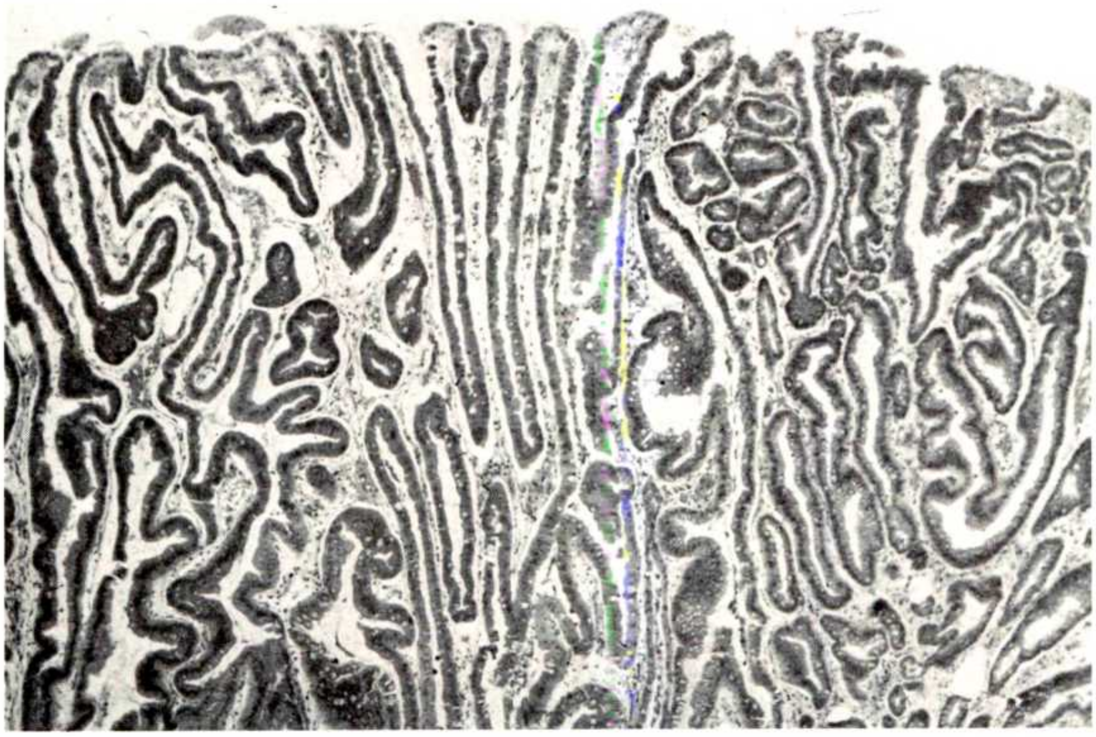


FIG. 3. Photomicrograph of tumor from Case Two. Brunner's glands are seen in the base. (Hematoxylin and Eosin × 100 original magnification)

and 2% of gastric polyps are villous tumors.[52] Sixty per cent of reported gastric villous tumors showed areas of adenocarcinoma.[52]

Three villous tumors of the ileum have been reported and all were benign.[6] There are eight reported cases in the jejunum,[30] three of which had invasive changes.

The present paper adds two cases of villous tumor of the duodenum to the 39 cases previously reported.[1,5,7,9,11,13,14,18–21,25,29–34,37,38,40,42,44–46,48,50,51,53] Of these 41 cases, 11 or 27% showed evidence of invasive changes.[13,14,25,32–34,40,44,48,51] This incidence compares closely with the percentage of invasive adenocarcinoma reported in the colon.

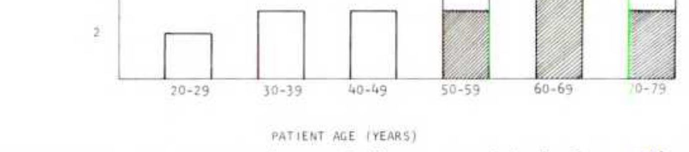


FIG. 4. Patient age in reported cases of villous tumor of the duodenum. The cross-hatched areas represent tumors with invasive carcinoma.

Villous Tumors of the Duodenum

Of the 41 cases reviewed, 24 (56%) were women and 17 (44%) men. The age range was 25–76 years (mean 57 years). Eighty per cent of patients were 50 years or older (Fig. 4).

The duration of presenting symptoms varied from four weeks[32] to sixteen years.[25] These included: 1) gastrointestinal bleeding of variable degree manifested by anemia, melena or hematemesis. This was present in eleven cases, three of which had major upper gastrointestinal bleeding.[29,30,33] 2) Obstructive symptoms, including frequent eructation or vomiting, were present in ten cases. 3) Obstructive jaundice was present in nine cases. 4) Vague dyspepsia was the presenting symptom in eight cases. 5) The lesion was an incidental finding on x-ray in two cases[20,37] and at autopsy in one case (21). Of note is that six patients had undergone previous surgical exploration for these symptoms before the diagnosis was established.[7,9,30,32,33]

Radiographic barium contrast evaluation of the upper GI tract was performed in 30 cases. These x-rays revealed the lesion in all but two cases.[30,33] Radiographically, the lesion appears as a filling defect with barium coating the interstices and appearing as a fine network in a palisaded or striated appearance.[40]

Endoscopy was performed in two cases.[20,46] Both of these lesions were in the first portion of the duodenum. In one case the lesion was red, strawberry-like and polypoid.[46] In the other case it was said to have the appearance of a colonic villous adenoma.[51]

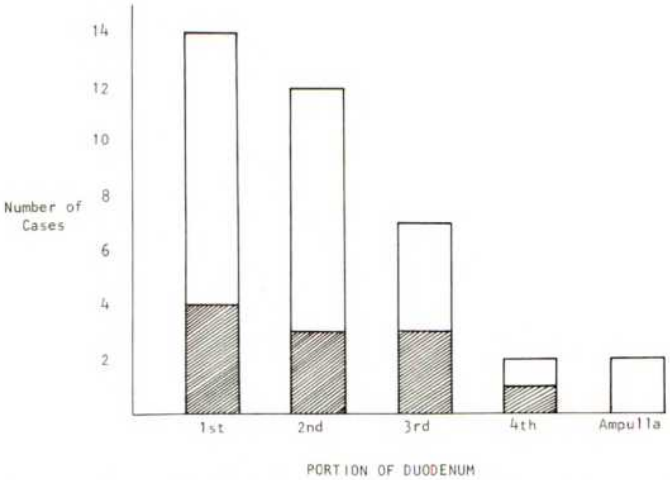


FIG. 5. Location of reported villous tumors of the duodenum. The cross-hatched areas represent tumors with invasive carcinoma.

Hypotonic duodenography may be useful and is the best method for obtaining air-contrast coating of a lesion.[40] It proved useful in Case 1 of our report. It should be mentioned that angiography in our Case 1 actually proved to be misleading.

Most villous lesions were in the proximal duodenum. There were 14 lesions in the first portion, 12 in the second, seven in the third and two in the fourth. There were also two lesions of the ampulla (Fig. 5). Of the two lesions in the fourth portion, one was an adenocarcinoma,[33] and of the seven in the third portion, three showed invasive changes.[14,37,40] The distal duodenum thus contained only 24% of reported lesions, but 44% of these showed invasive changes. There were four invasive lesions in the first portion[25,34,44,51] and three invasive lesions in the second portion (25%) (Fig. 5).[13,32] These figures may be the result of the less frequent early detection of benign lesions in the less accessible distal area of the duodenum.

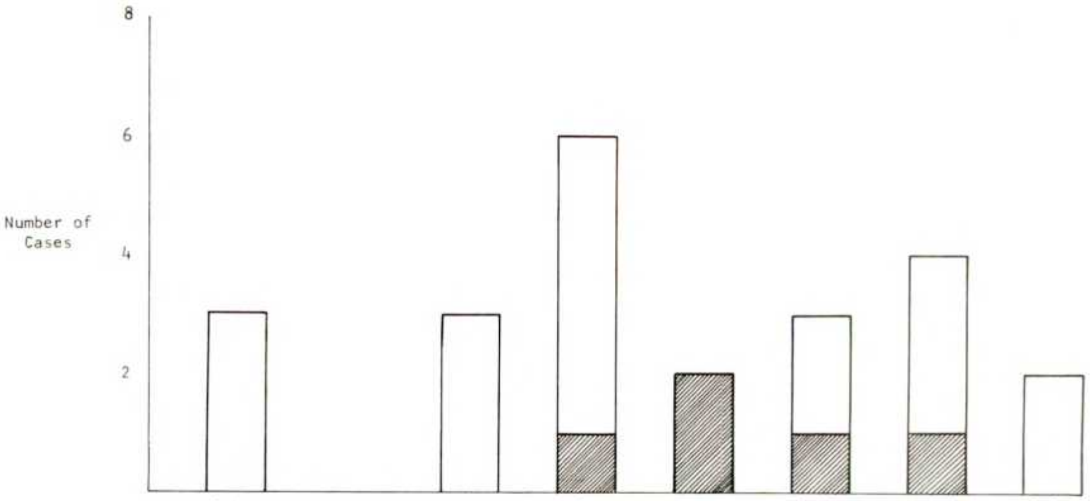
No malignancies were noted in patients under 50 years old. The incidence of invasive changes rises with age (Fig. 4). This contrasts with villous tumors occurring in the colon and rectum. Here, carcinoma has been reported at the age of 30 years[17] and the average age for invasive change in villous tumors is 55.[2,17]

There was no clear relationship between symptoms and invasive carcinoma. Five of nine patients who were jaundiced did not have invasive tumors.

The size of the lesion was reported in 23 of the 41 cases. This ranged from 4 mm [9,21] to 8.5 cm.[18] No lesions under 4 cm in size showed evidence of invasion. Of the remaining 17 lesions, five showed invasion (29%) (Fig. 6). In colorectal lesions, it also appears that the larger the lesion, the higher the incidence of malignancy.[2,36] However, 7–24% of villous tumors of the colon and rectum under 2 cm in size are reported to show invasive changes.[17,36]

Although rare, villous tumors of the duodenum are being diagnosed more frequently as a result of improved diagnostic techniques (Fig. 1). These tumors may give rise to bleeding, obstructive symptoms or jaundice. Duodenotomy and polypectomy are adequate surgical treatment for benign villous tumors. However, more radical excision may be indicated in the presence of invasive carcinoma. As a result of the development of fibro-optic endoscopy, histological evaluation of the surface of the lesion may be available. The possibility of invasive adenocarcinoma deep within the tumor must, however, always be considered. Although the gross characteristics of the tumor upon inspection and palpation are clearly of primary importance, this review of reported experience indicates that the incidence of invasive carcinoma is especially high in villous tumors of the distal duodenum, in those in patients over 50

FIG. 6. The diameter in centimeters of reported duodenal villous tumors. The cross-hatched areas represent tumors with invasive carcinoma.



years of age and in tumors exceeding 4 cm in diameter. Furthermore, these findings suggest that improved diagnostic techniques, and the removal of these lesions from patients who are younger and whose lesions are smaller, may reduce the incidence of invasive carcinoma.

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Experimental and Clinical Application of Microvascular Surgery

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The object of these studies was the development of a technique whereby a vessel of 1 mm or smaller could be easily anastomosed. In total replantation of rabbit ears, only 3 ears survived replantation in 80 attempts in the first series. In the second series of 80, 35 ears survived completely, 3 ears partially survived and 8 additional ears survived the postoperative period, but the rabbits died within 2 weeks due to diarrhea. Thirty-five ears failed and venous obstruction was the primary cause. Free transplantation of a great toe and a second toe to recreate a thumb is also described. The operative procedure of the great toe to thumb transplantation does not appear to be difficult. Six months after operation, the function of the newly created thumb was good. The second toe to thumb transfer was more difficult technically compared to the great toe to thumb transfer due to the much smaller size of the digital vessels of the second toe. However, removal of the second toe causes less disadvantage than the removal of the great toe. Nine months postoperatively, the function of the newly created thumb was satisfactory. Digital replantation is described with 36 cases with 65 complete finger amputations. Thirty-two with 45 fingers survived the reattachment. Repair of one artery per digit is sufficient, although two probably are better. A minimum of 2 veins per digit must be repaired. Prompt re-exploration is imperative if postoperative circulatory impairment occurs. In this group, arterial obstruction was more frequent than venous obstruction as the cause of replantation failure. The function of the replanted fingers is satisfactory in the majority of the cases.

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SINCE MICROSURGERY was pioneered by Jacobson and Suarez[12] in 1960, the work has been extended by others and the technique of microvascular replantation has been firmly established.[1-20] Total ear replantation of a rabbit utilizing microminiature vascular anastomosis was performed by Buncke and Schultz[2] in 1965. Experimental digital implantation and transfer of a free joint and composite tissue have been achieved by Buncke and associates.[3-5] Successful replantation of amputated arm[17] or digits,[11,14-16,18] reconstruction of a thumb by autotransplantation of the hallux,[10] free muscle transplanted with neurovascular anastomosis has been reported.[19]

In 1969, the author experimented with animals to develop the technique of microvascular surgery, and since 1971, replantation has been performed successfully in man. The results are described in this paper.

Replantation of the Rabbit Ears

The object of this experiment was to develop a technique whereby a vessel of one millimeter or smaller could be easily anastomosed. The central ear vessels of a rabbit weighing 2–2.5 kg fell within this critical range.

Technique

The rabbits were anesthesized with intramuscular or subcutaneous injections of Ketalar, 20 mg and 5 cc of 2% procaine was given locally. The central artery, vein and other subcutaneous veins were dissected free. After removal of the ear, it was immediately reimplanted by overlapping the cartilage 1 cm in length; the vessel anastomosis was carried out in 1–3 hours at room temperature. Total ischemic time ranged 3–5 hours.

The severed ends of the vein were approximated by double clamps and the blood and fibrin clots in the segment between the clamps were washed out with heparinized saline solution. The adventitia was detached completely for about 3 mm. in length and cut with scissors (Fig. 1). The vessel ends were approximated and microminiature repair was carried out under 16-25 magnification. Interrupted suture 8–10 stitches were performed on the anterior wall

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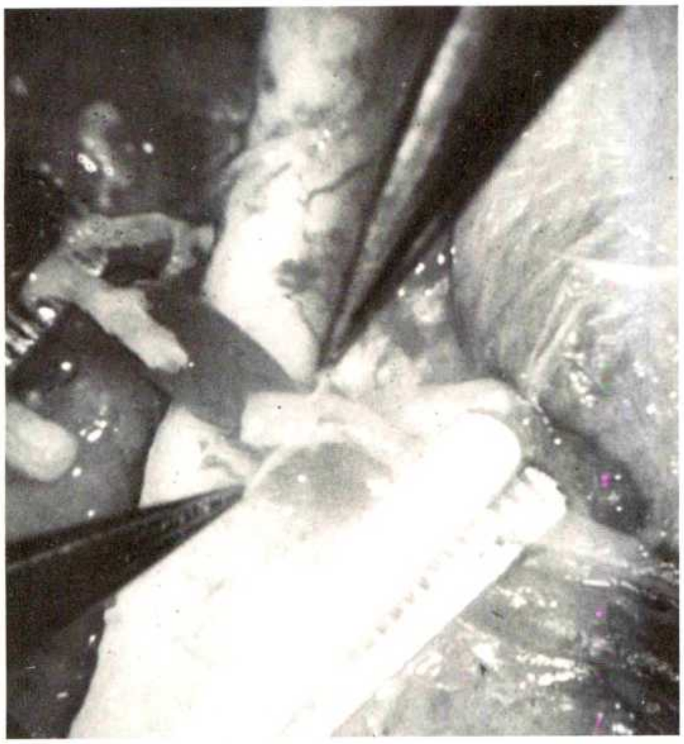

FIG. 1. The adventitia was stripped by the two forceps.

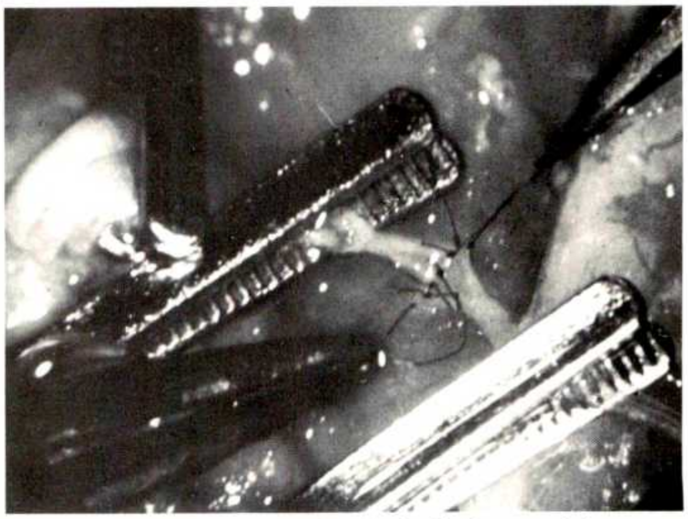

FIG. 2. The vein was approximated by the double clamps and the anterior wall was sutured.

from right to left (Fig. 2) using only one stay suture and the posterior wall was left completely free of suture. The clamps were then rotated and the posterior wall suturing was performed with 10(0) microfilament. After the anastomosis of two veins, arterial suture was performed in a similar manner (full layer suture). Angiographic studies two months after ear replantation are shown in Fig. 3.

No systemic anticoagulation was given but the rabbit received 50,000 units of penicillin intramuscularly per day for three days and was observed for at least two weeks.

Results

In the first series of 80 experiments, only three ears completely survived the transplantation. In the second series of 80 experiments, 35 ears completely survived and three ears partially survived. An additional eight ears survived the transplantation but the animals died of diarrhea within two weeks. Venous obstruction was the common cause of failure.

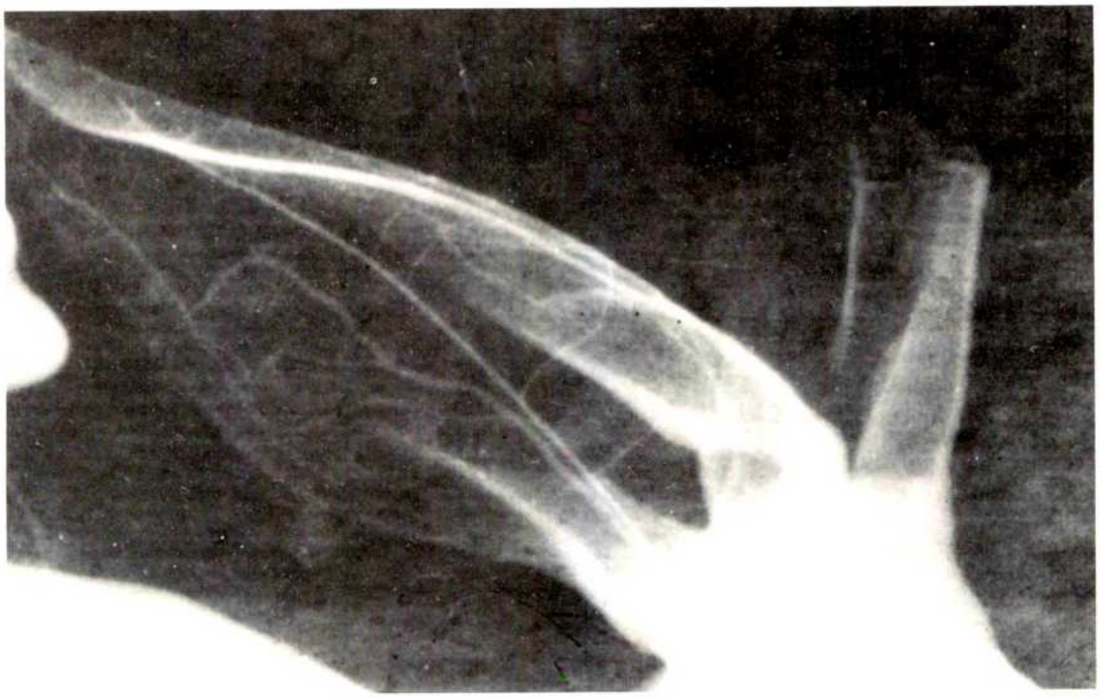

FIG. 3. Angiogram two months after replantation, artery and vein.

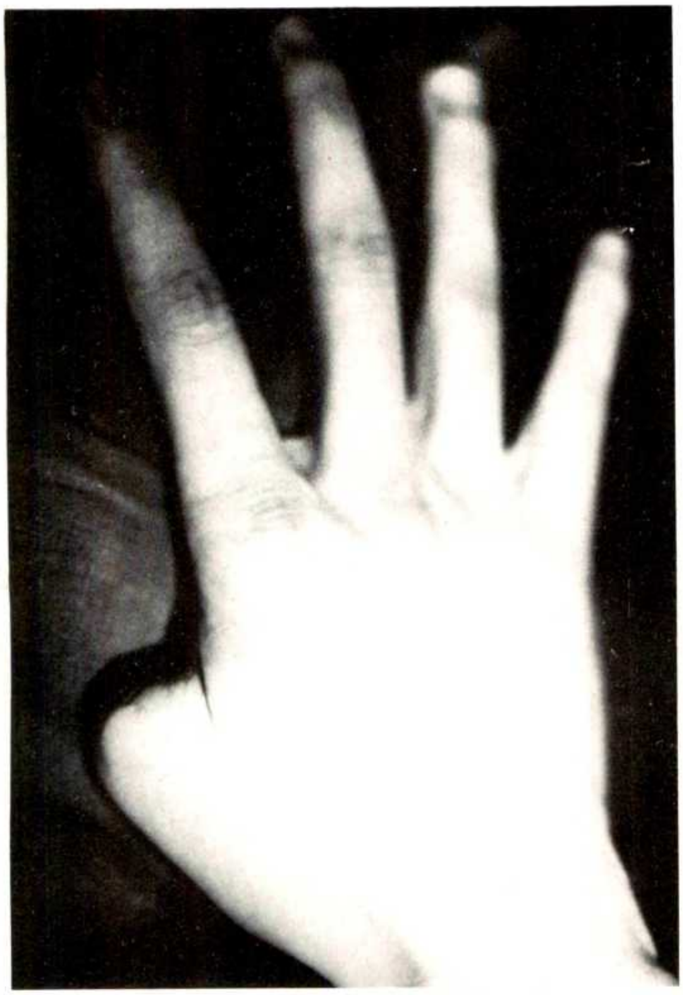

FIG. 4. Right thumb, amputating through the M-P joint.

Discussion

The poor result of the earlier experiment was due to the unfamiliarities of the microsurgical technique and improper suture material. In the later experiment, utilizing the technique as described, 35 ears survived completely in 80 attempts. Systemic heparinization was not given in these experiments. Since venous obstruction was the most common cause of failure, systemic heparinization or administration of low molecular weight dextran might have improved the results. The cardinal method of vessel anastomosis is to make the two stay sutures 120 degrees apart for the microsurgery, so that when the two stay sutures are tensed, the posterior vessel wall will lag behind the needle and will not catch it.[5] In venous repair, the posterior wall was caught when the needle was passed through the anterior wall; therefore, one stay suture at the right hand side of the vessel margin was used. After applying the stay suture, the second suture was inserted by grasping the left hand side of the vessel wall. The artery became very fragile after dissection of the adventitial layer; therefore, adjustable double clamps were essential to keep the vessel ends approximated to release the tension on the anastomotic line.

Free Transplantation of a Great Toe and Second Toe to Recreate a Thumb

Case Report

A 20-year-old male was admitted to Ho-ping Municipal Hospital on February 4, 1973. Three months prior to admission, he had injured his right thumb, amputating through the M-P joint (Fig. 4). After careful consideration, it was recommended that free transfer of his right great toe to thumb be performed.

On February 16, 1973, under general anesthesia, a tourniquet was applied to the right leg and the right great toe was explored at the distal metatarsal level. Two extensor tendons and one flexor tendon were dis-

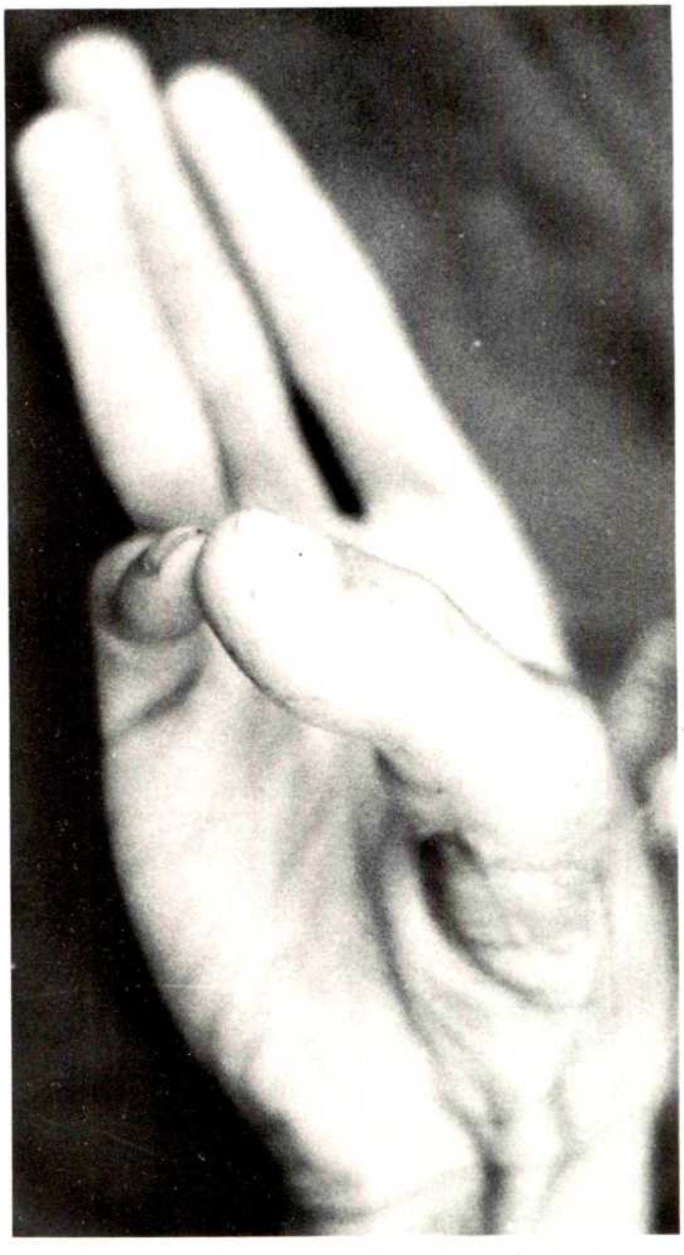

FIG. 5. Six months postoperatively. He has good opposition.

sected at the proximal portion about 10 cm in length; the fibular digital artery was isolated but the tibial digital artery was absent. The great toe was amputated at the proximal portion of the M-P joint and the wound was closed. The stump of the right thumb was explored; the digital vessels and the digital nerves were absent at the distal metacarpal level. The bone was shortened by about 1 cm and the bony part of the metatarsal was attached to the metacarpal by wire fixation. The extensor tendon was sutured to the extensor pollicis longus and brevis, and the flexor tendon was sutured to the palmaris longus. A branch of the radial artery was then isolated at the metacarpal base and united to the fibular digital artery by a 5 cm venous graft by microvascular anastomosis. Venous graft was necessary because the digital artery of the toe had been injured during arterial dissection. Excellent blood flow was obtained immediately and three dorsal veins were anastomosed. Because of the skin defect at both sides of the thumb, abdominal pedicle skin graft was performed. The total time of operation was 14 hours.

The patient was given heparin 5000 units intramuscularly every 6 hours for 24 hours, then dicoumarol 100 mg per day orally for two weeks. Postoperative course was smooth. Nerve graft was carried out six weeks after the operation. Eight weeks postoperatively, he had good pinch and opposition; while the sensation was still absent, he was able to write, eat with chopsticks and grasp objects with his new thumb. Six months postoperatively, active motion of the M-P joint was limited, IP joint flexion was about 30 degrees but extension was only a trace, similar to a mallet finger (Fig. 5). He had stereognosis of coin and recognition of pin prick; pain and touch sensation were present. Two points discrimination at the tip of the thumb was about 1.5 cm and he had the ability to distinguish hot and cold water. The stump of the amputated toe healed completely and he worked as a taxi driver without difficulty.

Case Report

A 17-year-old male suffered a machine crush injury, amputating the thumb which could not be treated by replantation. The index, middle and ring fingers were amputated at the middle phalanx level with severe injury to the proximal phalanx, and the little finger was amputated at the proximal phalanx. The patient was treated by abdominal pedicle graft to reconstruct the index, middle and ring fingers, and toe to thumb transfer was carried out.

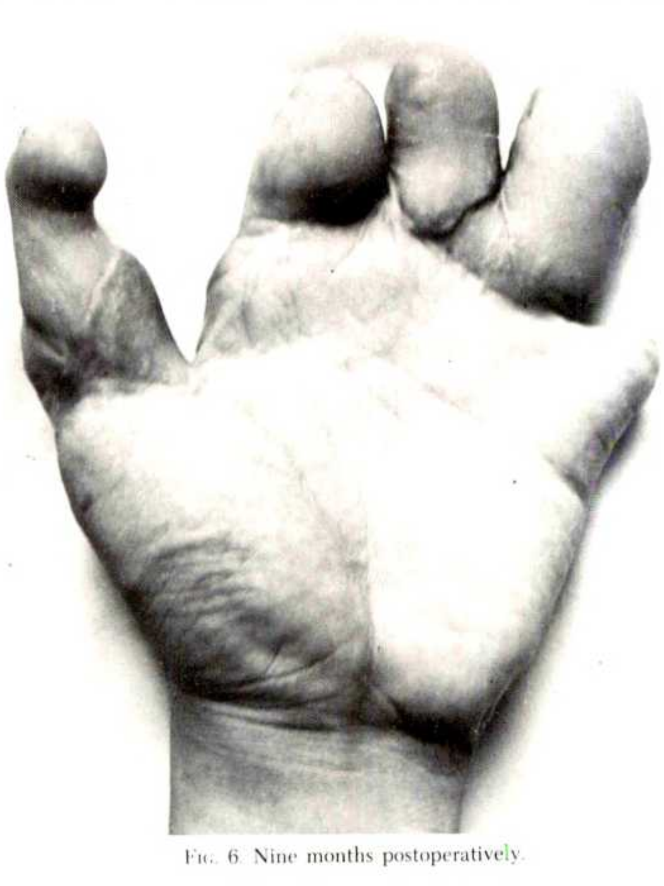

Fig. 6. Nine months postoperatively.

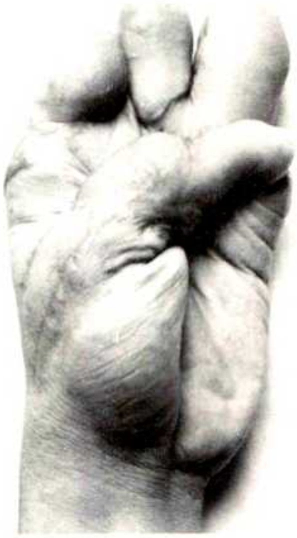

Fig. 7. Patient can touch the stump of the little finger with the new thumb.

On August 14, 1973, under general anesthesia, a tourniquet was applied to the left leg. The left second toe was explored at the M-P joint level; two extensor tendons and one flexor tendon were dissected at the proximal portion, about 10 cm in length. Both tibial and fibular digital arteries were identified and dissected. The joint was disarticulated and enough skin was left to cover the stump of the amputation. Both digital nerves were dissected at the proximal portion, about 3 cm in length; the second toe was then transplanted to the thumb stump. The size of the second toe digital artery was about 0.6 mm in diameter and eight stitches suture with 10(0) microfilament were done.

Four small veins were then anastomosed, all by venous graft about 5 cm in length, to bridge the defect. The digital nerves were anastomosed by funicular suture, and skin defect at the dorsal and both sides of the new thumb were covered by abdominal pedicle graft. The total operative time was 13 hours.

The postoperative course was smooth. Three weeks postoperatively, the abdominal pedicle graft was detached and the patient was discharged one month after the operation. When examined nine months postoperatively, he had good pinch while the flexion of the M-P joint was 60 degrees and IP joint was 30 degrees (Figs. 6 and 7). He had touch and pain sensation and walked without a limp.

Discussion

Toe to thumb transfer by immediate Nicoladoni procedure[3] as described in the present cases requires long operative time. However, if successful, the new thumb is very useful.

The operative procedure of toe-to thumb transplantation does not appear to be difficult; however, the second toe to thumb transfer operation is more difficult technically because the digital vessels of the second toe are about half the size of those of the great toe. Since removal of the great toe causes certain disadvantages, the second toe was chosen for transplantation in case 2.

TABLE 1. *Summary of 36 Cases of Complete Finger Amputation*

Case No.	Age (yrs.)	Sex	Site of Amputation	Survived	Failed
1	28	M	Rt. 2 m-p (3, 4 m-p)		2
2	21	F	Rt. 1 m-p		1
3	20	M	Rt. 5 m-ph		5
4	25	M	Rt. 5 p-ph		5
5	20	M	Rt. 3, 4 m-ph	4	3
6	24	M	Rt. 3, 4, 5 m-p	3, 4, 5	
7	17	M	Rt. 3, 4, 5 m-ph	3	4, 5
8	28	M	Rt. 3 m-ph	3	
9	53	M	Rt. 1 p-ph 2, 3, 4 m-p	1	2, 3, 4
10	18	M	Lt. 3 p-ph	3	
11	20	M	Rt. 5 p-ph	5	
12	26	M	Rt. 1 p-ph	1	
13	25	F	Lt. 2, 4 DIP 3 m-ph	2,3	4
14	18	F	Rt. 2 m-ph	2	
15	20	F	Rt. 4 m-ph 5 DIP	4	5
16	44	M	Lt. 1, 2, 3 p-ph (4, 5 m-ph) Rt. 1 p-ph	Lt. 1, 2, 3	Rt. 1
17	20	M	Lt. 3 p-ph	3	
18	17	M	Lt. 3 DIP (4)	3	
19	18	M	Lt. 4 m-ph	4	
20	18	M	Lt. 1 m-p	1	
21	19	M	Lt. 4, 5 m-ph (3)	4	5
22	20	M	Rt. 1 p-ph	1	
23	18	M	Rt. 3 m-ph (4)	3	
24	20	M	Rt. 1, 2, 3 p-ph	2, 3	1
25	23	M	Rt. 2, 3 m-ph	2, 3	
26	20	F	Rt. 2 m-ph	2	
27	20	M	Rt. 2, 3 m-p	2, 3	
28	18	M	Lt. 2, 3, 4, 5 p-ph	2, 3	4, 5
29	17	F	Lt. 3 m-ph	3	
30	28	M	Rt. 2, 3 p-ph	2, 3	
31	35	M	Lt. 2, 3, 4 p-ph	2, 3, 4	
32	14	M	Rt. 1, 2 p-ph	1	2
33	19	M	Rt. 3, 4, 5 m-ph	5	3, 4
34	25	M	Rt. 2 m-p (1, 3)	2 (index to thumb)	
35	16	M	Rt. 4, 5 m-p	4, 5	
36	8	M	Lt. 5 m-ph	5	
Total 38 cases			65 fingers	45 fingers	20 fingers

Numbers 1, 2, 3, 4, 5 represent the thumb, index, middle, ring and little fingers, respectively.

( ) = without replantation.
m-p = metacarpa-phalangeal joint.
PIP = proximal interphalangeal joint.
DIP = distal interphalangeal joint.
p-ph = proximal phalanx.
m-ph = middle phalanx.

Digital Replantation

Materials and Method

From August, 1972 to November, 1973, 30 cases of incomplete amputation and 61 cases of complete amputation, including the upper arm, forearm, wrist and palm, finger level were treated. Thirty-six cases with 65 complete fingers amputation are included in this report (Table 1).

When the finger was amputated, it was cooled by ice in a plastic bag and sent to the hospital as soon as possible. After it was cleaned by scrubbing, it was immersed in normal saline solution and kept in the ice box at 0-4 C.

The indication for reattachment was minor crushed wound or clear-cut amputation within 12–14 hours of anoxia.[16]

Operation was carried out as soon as possible under brachial plexus block or endotracheal anesthesia. Air tourniquet was applied on and off during the operation.

After debridement was carried out to clean the contusion, bone was shortened about half to one centimeter and was united by intramedullary pin fixation. Flexor tendon was united by 4 ("0") nylon suture, one to two arteries were anastomosed by microvascular suture technique and two digital nerves were approximated by one stitch suture. The tourniquet was then released and the site of anastomosis was checked. The finger became pinkish immediately and venous return was profuse. Finally, closure of the volar skin was performed.

The tourniquet was then reapplied to control the bleeding and anastomosis of extensor tendon was done by two or three stitches. The dorsal subcutaneous veins were anastomosed by intermittent suture by 10 ("0") or 8 ("0") microfilament.

At least two veins were united, usually 2–5 veins were anastomosed. The tourniquet was released again and the site of anastomosis was checked and the dorsal skin was closed. If multiple fingers were amputated, the same procedure was applied again.

During the operation, the vessel stump was irrigated with heparinized saline and magnesium sulfate (1000 units of heparin in 100 cc of normal saline and 20 cc of 10% magnesium sulfate solution) and the patient received 5000

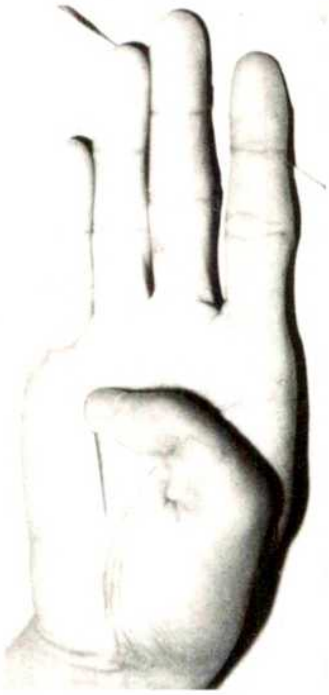

FIG. 8. Case 12. Followup eight months postoperatively. Note flexion of thumb.

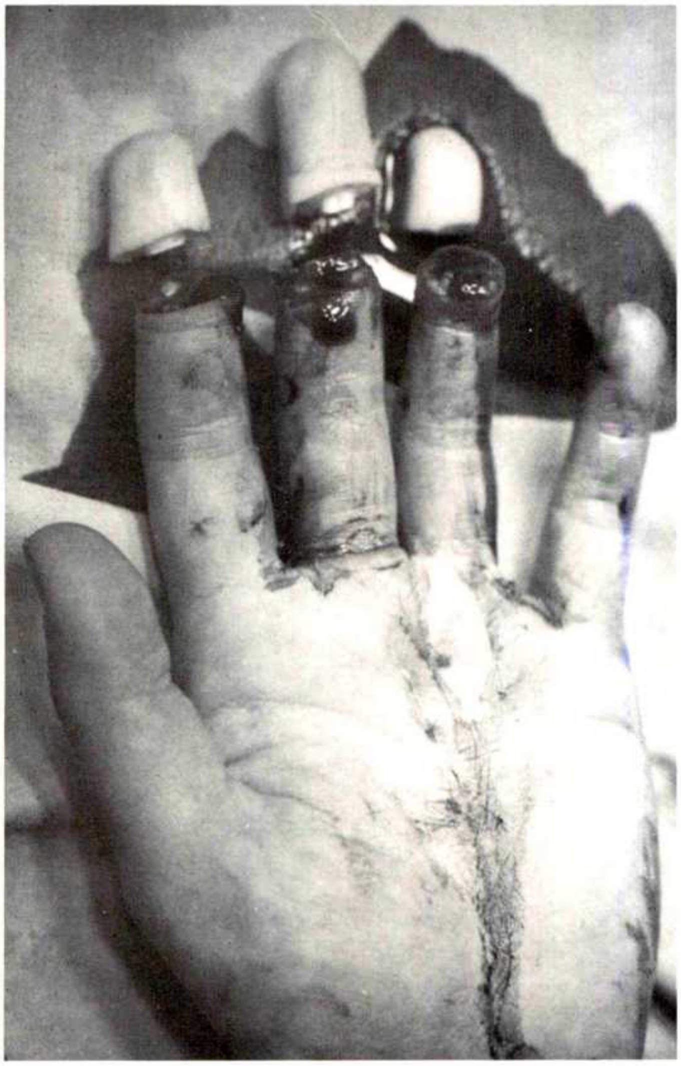

FIG. 9. Case 13. Left hand, prior to operation.

units of heparin every 6 hours for 24 hours. Perfusion of the amputated finger was not done. In recent cases, 500 cc of how molecular dextran was given intravenously daily for two weeks. Other medication includes coumadin, antibiotics, complamine, anginin, etc.

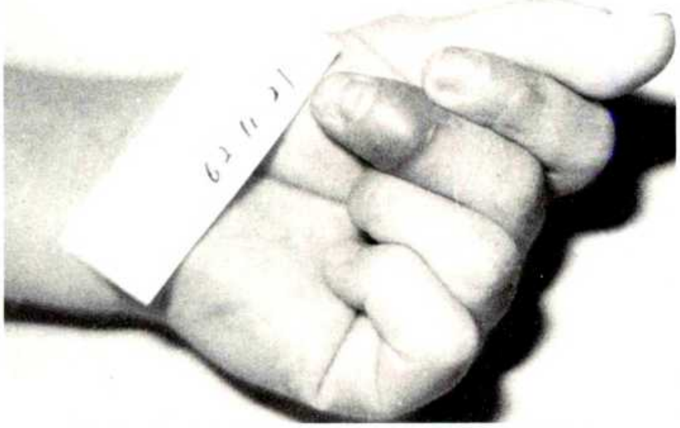

FIG. 10. Case 13. Left hand, six months postoperatively.

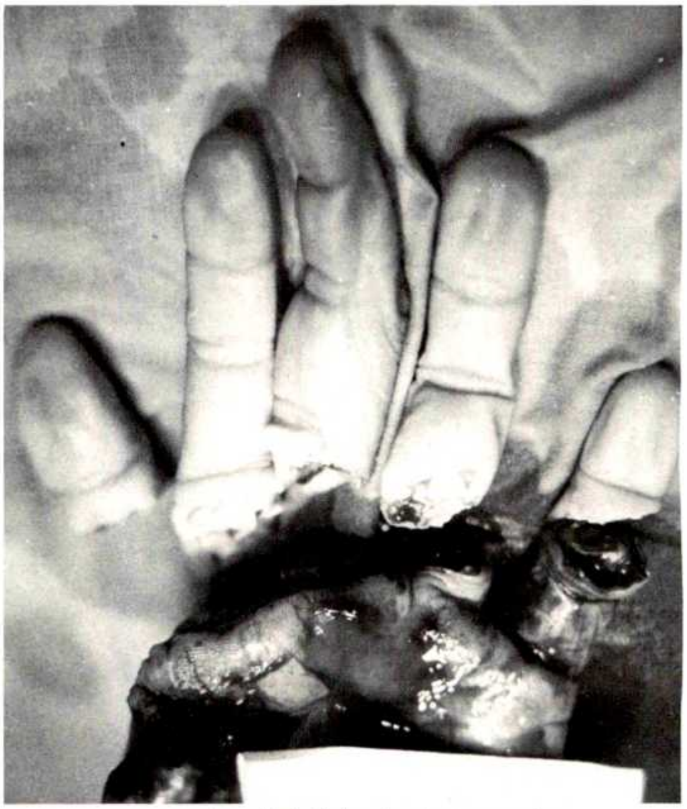

FIG. 11. Case 16. Left hand, prior to operation.

If any sign of cyanosis, coldness or pallor developed, the wound was re-explored. Arteries were checked first; if they were patent, the vein was checked again. The thrombosed vessel was resectioned and resutured or repaired by venous graft.

Results

The site of amputation of the fingers were 4 at DIP, 22 at middle phalanx and 39 between PIP and M-P. The survival rate was 50%, 68.1% and 72%, respectively (Table 1).

Case Reports

Case 12. A 26-year-old male suffered guillotine amputation of the right thumb at the IP joint level on April 16, 1973. Replantation was carried out by fusion of the IP joint, repair of two digital arteries, two digital nerves and three veins. Postoperative course was smooth; patient was discharged two weeks following operation and was examined on December 10, 1973. Two point discrimination of the thumb tip was 1 cm., temperature detection was good and motion of the thumb was normal except that the IP joint was in 30 degree flexion (Fig. 8).

Case 13. A 25-year-old female, in her third month of pregnancy, suffered amputation of the left index, middle and ring fingers at the DIP joint level by accident on May 25, 1973, at 6:00 p.m. (Fig. 9). She came to the hospital about 30 minutes after the accident and replantation was carried out under brachial block anesthesia.

The index finger was replanted first by the usual method; two arteries, two nerves and three veins were repaired and the DIP joint was fused. Inadvertently, the middle and ring fingers were cooled to minus 20 C and were stony hard. After immersing in saline for a period of time, the same procedure for replantation was performed on the middle and ring fingers.

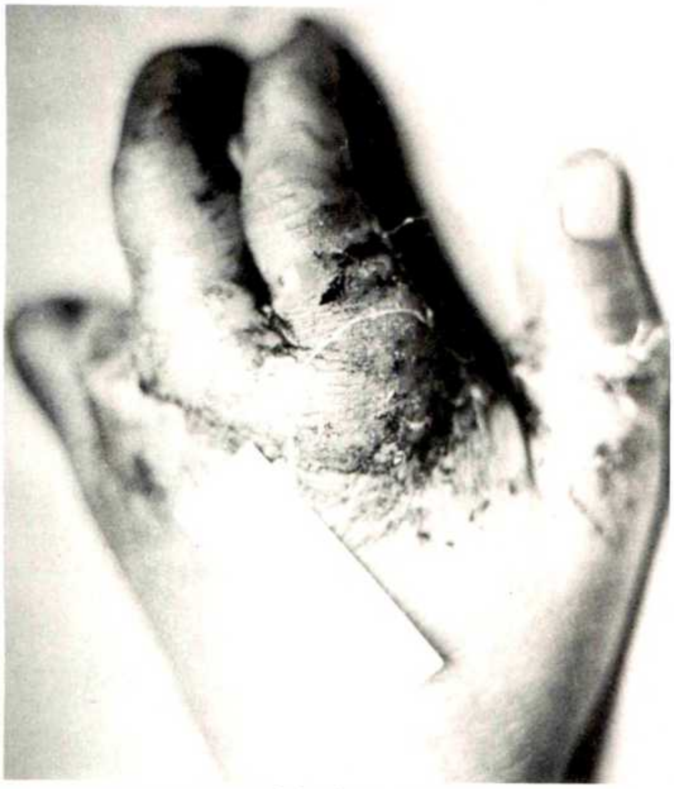

FIG. 12. Case 16. Left hand, two weeks postoperatively.

The ring finger developed cyanosis 24 hours later and was amputated. The color and temperature of the middle finger was not as good as that of the index finger; however, it survived two weeks after the operation. Six months later, both index and middle finger tip still showed hyperemia (Fig. 10).

Case 16. A 44-year-old male had both hands cut by a paper machine at 8:00 p.m. on September 21, 1973, with amputation of all fingers of the left hand and the right thumb, and partial amputation of the right index finger (Fig. 11). Replantation was carried out at 9:30 p.m. and completed at 7:00 a.m. the following morning.

Two arteries, two nerves, two veins and the extensor tendon were repaired on the left thumb. The left index finger was replanted by anastomosis of two arteries, two nerves, two veins and the extensor and flexor tendons.

The left middle finger was replanted by anastomosis of one artery, one nerve, two veins and extensor and flexor tendons.

The right thumb was replanted last by anastomosis of one artery, one nerve, two veins and the extensor tendon.

Immediately after replantation, all fingers became pinkish and warm. On September 25, 1973, the right thumb became moderately swollen, mildly cyanotic and cold. It was found that the dressing was too tight at the base of the right thumb. The dressing was released and the color improved a little. Two days later, the thumb became cyanotic and was finally amputated on October 2, 1973.

The left thumb, index and middle fingers survived over two weeks (Fig. 12).

Case 34. A 25-year-old male was caught by an electric saw at 9:30 p.m. on June 8, 1973, and referred to our hospital an hour later. The left thumb, index and middle fingers, and the thumb index web were amputated (Fig. 13). The amputation stump was clean but only the index finger was suitable for replantation.

Under brachial block anesthesia, excision of the proximal part of the phalangeal bones of the index finger and the middle finger was performed. Fixation of the proximal phalanx to the first metacarpal bone was performed by one Kirschner's pin. Primary suture of the flexor profundus to the flexor policis longus was performed. Two arteries were united, the extensor tendon was approximated to the thumb extensor tendon and four veins were repaired. The skin and soft tissue of the middle phalanx was covered to the thumb web. On the second day, cyanosis developed due to thrombosed arteries which were excised and repaired by a 2 cm venous graft and circulation was restored. Thereafter, the postoperative course was smooth. The patient was discharged on July 23, 1973.

Patient was readmitted on August 13, 1973, for tendolysis of the extensor tendon and neurovascular island graft of the ring finger to thumb. He could make good pinch with the new thumb, flexion of M-P was 90 degrees and IP was 30 degrees; the sensation was almost normal. When examined in December, flexion of the new M-P joint was 100 degrees and the IP joint remained at 30 degrees (Fig. 14). The patient could make precision grip, pain, touch and temperature sensations were nearly normal at the finger tip area. He returned to his regular work.

Case 36. An 8-year-old boy suffered from avulsion amputation of the left little finger at 10:00 a.m. on November 28, 1973, when he was trapped by an escalator. He was admitted to the hospital at 11:00 a.m. The middle phalanx was crushed and the soft tissue was also contused (Fig. 15).

Under general endotracheal anesthesia, replantation was performed by excision of the contused part of the soft tissue and total removal of the middle phalanx. Two arteries, two digital nerves and four veins were repaired. Total operative time was five hours. The finger was warm and pinkish until December 6, 1973, when it became cyanotic. Low molecular dextran, 250 cc intravenously per day, was given for one week. The finger again became

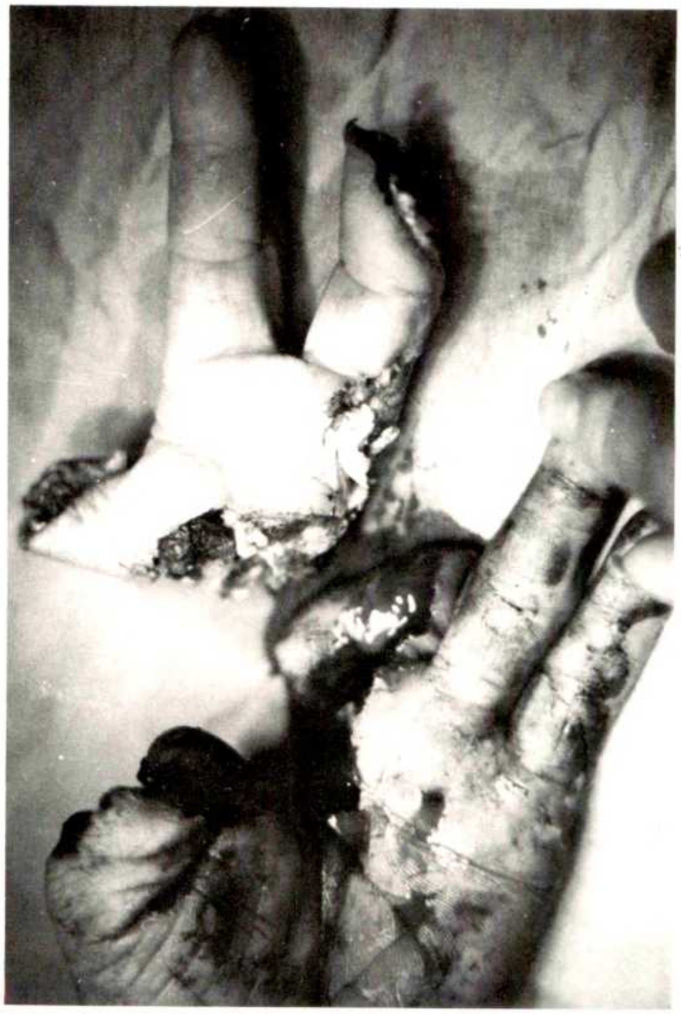

FIG. 13. Case 34. Left hand, prior to operation. Note amputation of thumb, index and middle phalanges. Only the index finger was sutable for replantation.

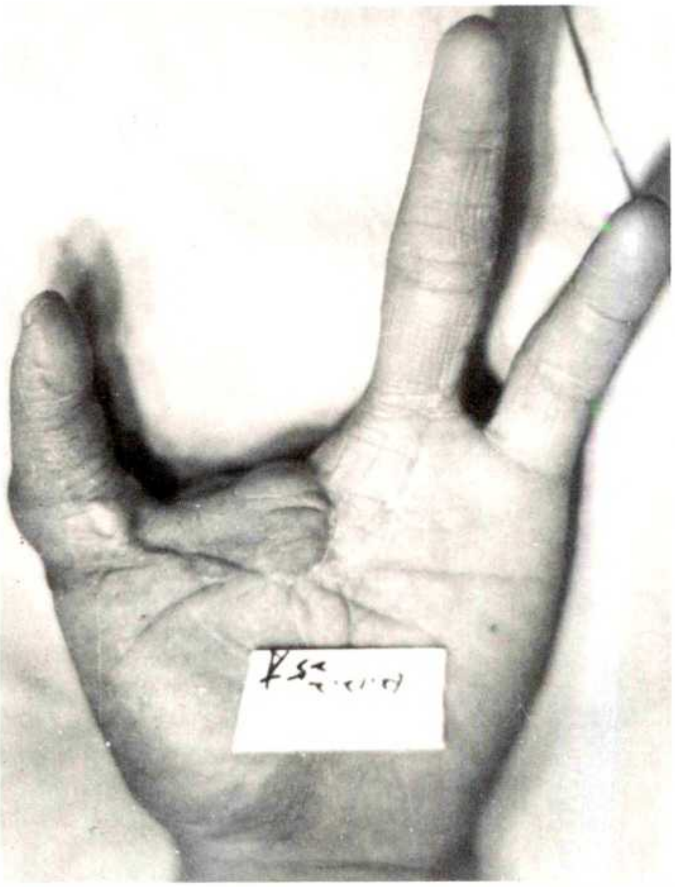

FIG. 14. Case 34. Left hand, six months postoperatively. Extension of thumb is complete.

pinkish and warm on December 7, 1973, and he was discharged two weeks postoperatively (Fig. 16).

Discussion

In the present series of 36 patients with 65 amputated fingers, 32 cases with 45 fingers surviving the reattachment. The successful rate of cases with at least one finger surviving the reattachment is 88%, while the survival rate of the total number of fingers is 69%. O'Brien[18] reported eight cases with 14 fingers receiving replantation and five cases with 11 fingers surviving the reattachment. The survival rate is 83%; however, a number of amputated fingers were not replanted.

The long operating time and the restriction of anoxia time are the main problems in digital replantation. The ideal technique should not only be uniformly successful but should also be easy and quick so that multiple fingers replantation becomes possible within the maximal limit of anoxia time.[1] Malt has estimated that the permissible period of replantation using hypothermia may be up to 18 hours.[17] Active blood flow and viability have been shown to return after 14 hours of anoxia.[18]

The operative time for one finger replantation is usually 2–3 hours with the aid of tourniquet control which is half the time in other series ranging 3–7 hours.[11,18]

Under the air tourniquet control, blood flow is still present but the bleeding is minimal; therefore, the operative field is clean and the vessel can be anastomosed quickly. For multiple fingers replantation, the air tourniquet is inflated for one hour, then deflated for 20 minutes. If the amputation is distal to proximal interphalangeal joint, rubber band tourniquet can also be used.

At present, it is possible to anastomose vessels of 0.5 mm in external diameter.[18] Sometimes, open anastomosis is necessary for the 0.3–0.5 mm vessel in children or about

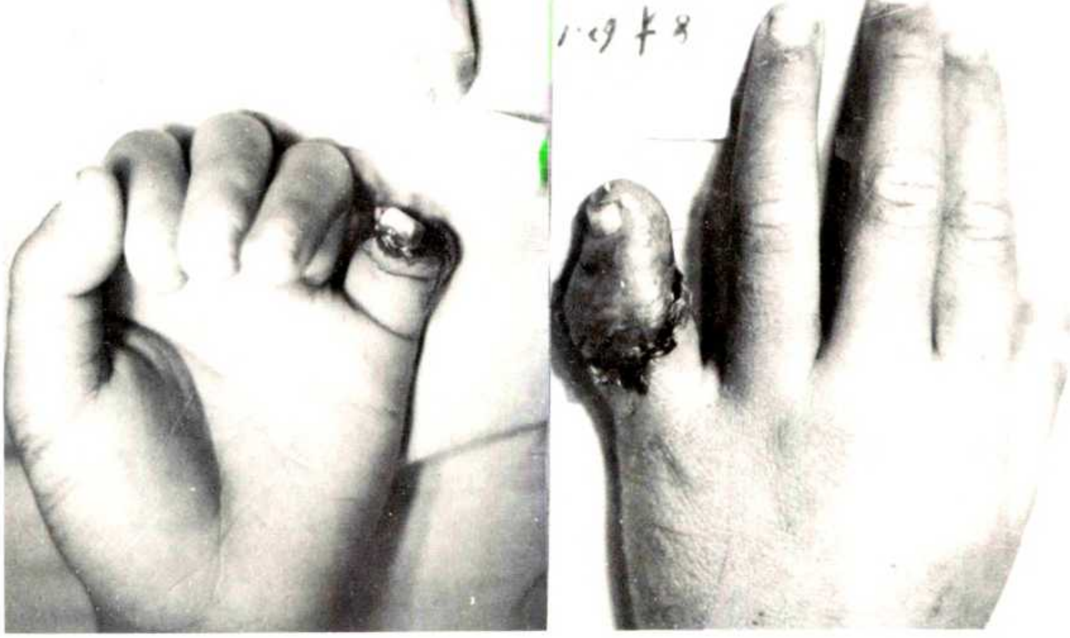

FIG. 15. (left) Case 36. Left hand, prior to operation. Fig. 16. (right) Left hand, two weeks postoperatively.

DIP level of finger. This is especially true for the small vein which cannot be separated for a suitable length to be applied by the double clamp.

Debridement of the contused part should be performed before shortening of bone. The bone is shortened by 0.5–1 cm or more, which is shorter than the soft tissue so that the vessel and nerve can be repaired without tension. If vessel defect is noted, venous graft should be applied.

Venous thrombosis is mentioned as the most frequent cause of replantation failure.[14,18] However, in this series, arterial obstruction was more frequent than venous obstruction. Twice as many veins were sutured as compared to arteries.

Although it has been reported that repair of two digital arteries would not increase the survival rate as compared with repair of single digital arteries, repair of two arteries and more than two veins may ensure a greater chance of survival.[18] When twice as many veins as arteries are sutured, the swelling is kept to a minimum and no decompression of digits is required.

Pallor, blanching and inadequate capillary filling are the main manifestations of arterial obstruction while venous obstruction shows mottling, dark purple discoloration and capillary filling remains.[14,18] Occasionally, cyanosis by venous regurgitation is noted in arterial obstruction.

Acland used the isotonic solution of magnesium sulfate in water to prevent early thrombosis formation at the site of anastomosis.[1] Magnesium sulfate is the ideal vasodilator and is strongly antithrombotic. Small amounts of magnesium sulfate solution in heparinized saline is beneficial.

Irrigation of the amputation stump is performed routinely but is not performed in the detached fingers because insertion of the needle may damage the arterial intima. The artery is united first. Allowing the veins to bleed permits early resumption of arterial flow, and shortens the period of tissue anoxia. In addition, the veins stand out when filled facilitating identification and repair. Systemic use of heparin and low molecular weight dextran during the operation may prevent early thrombosis. It is claimed that the frozen finger may be damaged as in frostbite and is contraindicated for replantation;[14] however, one frozen finger survived the replantation (case 13) without any tissue damage as compared to the non-frozen finger.

Consideration should also be given to autotransplantation of an amputation stump on top of another amputation stump,[18] as presented in case 34.

Evaluation of the functional result is difficult because of variation in the ages of the patients, the sites of amputation and the mechanism and extent of injury. Consideration must be given to the patient's occupation, his motivation and whether the long-term disability and numerous operative procedures will be worthwhile.

Since no upper extremity prosthesis is better functionally than a pinching or grasping hand with sensation, limited as it may be, every effort should be made to reimplant in the case of distal amputation of the fingers, especially the thumb and index finger.[14]

Although the followup period is relatively short in the present series, the function of the replanted finger is satisfactory in the majority of cases.

Acknowledgments

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A Gastroplasty for Short Esophagus and Reflux Esophagitis:

Experimental and Clinical Studies

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A safe, simple, effective gastroplasty for short esophagus with reflux esophagitis is described. It has been evaluated in dogs for up to three years with flexible fiberesophagoscopy, esophagrams and intraluminal pressure studies. Successful clinical experience has been encouraging.

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THE TREATMENT of reflux esophagitis in the presence of a short esophagus has two objectives: 1) the mechanical restoration of a one-way valve mechanism; and 2) infradiaphragmatic placement of the valve. In the presence of short esophagus the Collis gastroplasty corrects the shortening by using the lesser curvature of the stomach for extra length. Long term results have been excellent with the initial Collis procedure[1,2] or the addition of Belsey repair to the Collis technique.[4,5]

In the original Collis procedure, the stomach is divided 6–10 cm parallel to the lesser curvature, and a prolongation of the esophagus is achieved. In doing so a 12–20 cm suture line is created, which takes 45–60 minutes to accomplish. This technique inherently carries the possibility of a leak.

A modification of the Collis technique has been worked out in the dog and successfully applied clinically. The new technique has been found safer, simpler and effective. Moreover it reduces the operating time by 45 minutes.

Technique

A simple cartridge of two rows of staples is placed with the TA-55 stapler on the fundus of the stomach parallel to the lesser curvature. The lumen of the esophagus and of the new lesser curvature segment is held open by a perorally introduced esophageal dilator of French 44 to 55 size. An additional 6 cm of esophageal length is thus obtained (Fig. 1A).

This procedure takes one minute to perform. Next, the remaining gastric fundus is wrapped either totally or subtotally around the newly created tubular prolongation of the esophagus. Frequently, this entire valvular mechanism can be sutured in its entirety below the diaphragm (Fig. 1D).

Experiment

Esophagogastric incompetence was produced in a group of 8 dogs by either esophagogastrostomy or esophagogastromyectomy.[3,6] In a second operation esophageal lengthening and fundoplication was performed as described above.

In an additional 10 dogs the above two stages were performed simultaneously.

The effectiveness of this new gastroplasty was tested by pre- and postoperative photographic flexible fiberesophagoscopy, esophagrams, fluoroscopy and by gastroesophageal pressure studies.

Experimental Results

Two of the Group I dogs died, one of pneumonia and one of too narrow lesser curvature channel. The adequacy of the new channel was subsequently ensured by the insertion of the esophageal bougie during the stapling and fundoplication.

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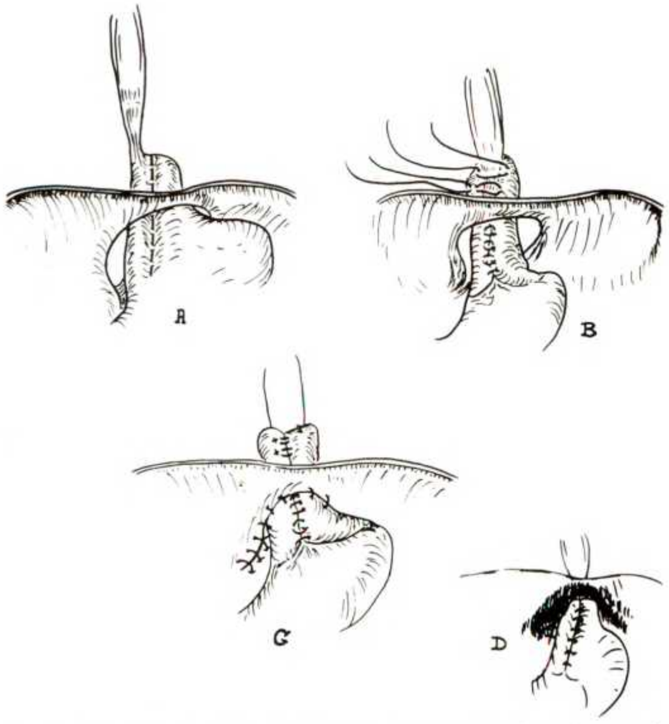
* Dr. Smith is a medical student whose research fellowship was supported by the New Jersey Medical School Class of 1972.



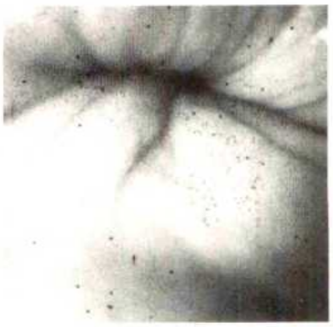


FIG. 2. Lower esophageal competence.

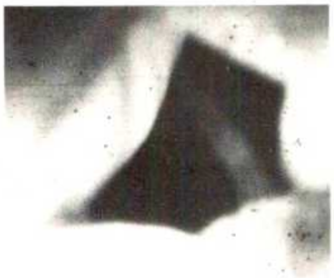


FIG. 3. Adequate lumen of new lower esophageal segment.

FIG. 1. A. Stapling parallel to the lesser curvature to lengthen short esophagus. B. Fundoplication. C. Suture of the hiatus: part of the plicated segment remains above the diaphragm. D. Frequently, the entire plicated segment can be sutured below the diaphragm, even if the true cardia is preoperatively at or above the level of the hiatus.

Complete healing of the hemorrhagic and/or ulcerating esophagitis was observed in the remaining six dogs of Group I. The Group II dogs never showed esophagitis. All surviving dogs maintained competence (Fig. 2) and a good size lumen (Fig. 3) during a three- year followup.

Pressure competence of the new sphincteric mechanism was routinely observed (Fig. 4).

Barium studies revealed a 5–6 cm competent lower esophageal segment (Fig. 5).

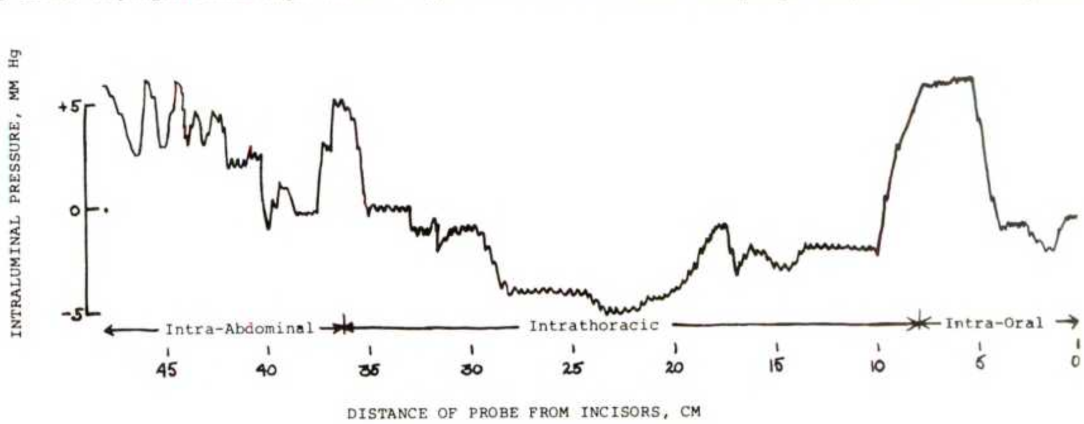
Case Reports

Case 1. A 56-year-old woman had two episodes of subacute but massive upper gastrointestinal bleeding. Lower esophageal hemorrhagic erosion was seen on fiberesophagoscopy. Barium swallow revealed a large sliding hiatal hernia (Fig. 6). The new gastroplasty and fundoplication was performed through the left seventh intercostal space. Postoperative esophagram revealed sphincteric competence and an infradiaphragmatic lower esophageal segment (Fig. 7). She has remained asymptomatic for over nine months, and fiberesophagoscopy has revealed healing of the esophageal erosions.

Case 2. A 65-year-old man had several episodes of dysphagia over the past few years. X-rays demonstrated a large hiatal hernia with about one-third of his stomach displaced in the chest. At operation a short esophagus was also found. A gastroplasty and fundoplication were performed through the left seventh intercostal space. He made an uneventful recovery and has remained free of dysphagia over several months.

Case 3. A 60-year-old woman has had severe epigastric pain and substernal burning recurring shortly after a hiatal hernioplasty performed 4 years previously elsewhere. Fiberesophagoscopy revealed free gastroesophageal reflux. Biopsies of the cardia revealed acute and chronic inflammation. Through the left seventh intercostal space, a gastroplasty and fundoplication were performed. A short esophagus was present. The entire plicated segment was sutured at an infradiaphragmatic position, even though the

FIG. 4. Manometric study of upper GI tract in preparation with myectomy and gastroplasty. See high pressure zone at the cardia after the gastroplasty.



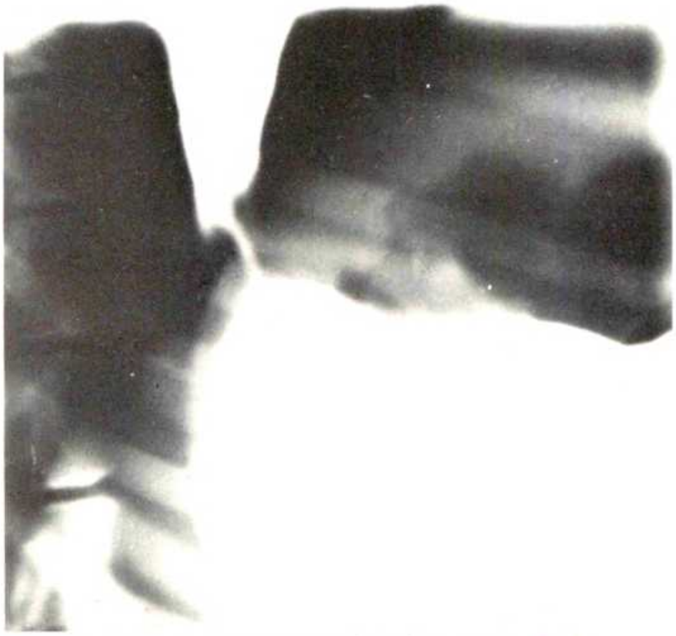


FIG. 5. Competent lower esophageal segment in the dog.

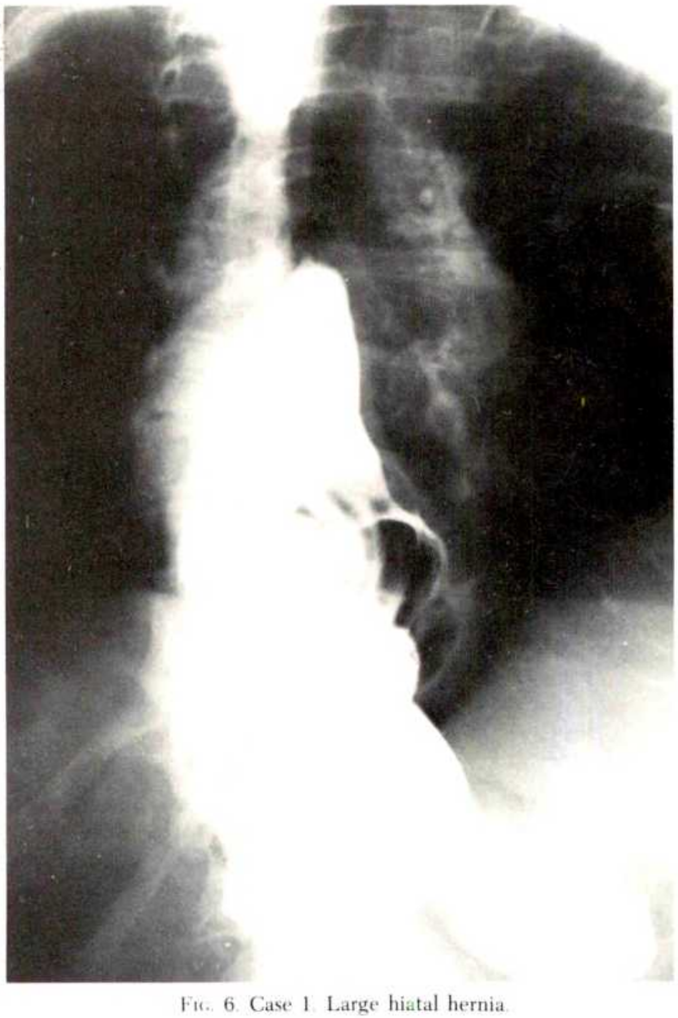


FIG. 6. Case 1. Large hiatal hernia.

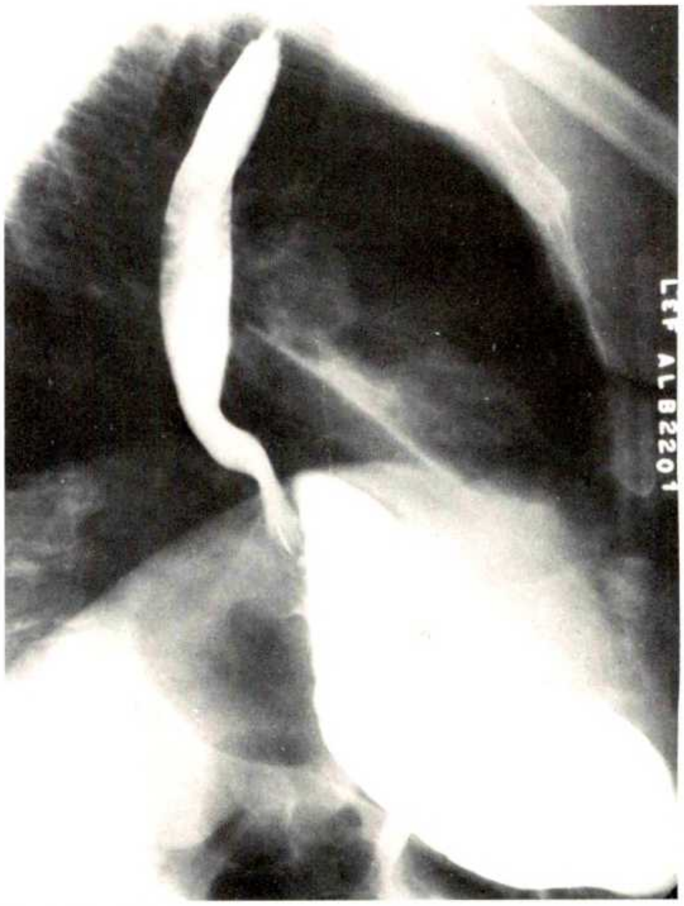


FIG. 7. Case 1. Competence of the lower esophageal, intra-abdominal segment after gastroplasty and fundoplication.

cardia could be pulled down only to the level of the diaphragm. She has remained free of pain for several months.

Comment

Great advances have been recently made in the treatment of reflux esophagitis. In the absence of esophageal shortening, simple transabdominal or transthoracic repair restores an intra-abdominal esophageal segment and transfixes the cardia below the diaphragm.

Long-standing esophagitis may produce not only circular intraluminal stricture but longitudinal shortening. The presently described technique produces a prolongation of the esophagus and fixation of the last few centimeters under the diaphragm. The gastroplasty produced by stapling is quick, safe and effective. The addition of the fundic wrapping effects a soft, cushioned but distensible collapse of the new esophageal segment. Moreover, it maintains the desired angle between the esophagus and the stomach and helps by its bulk to transfix the last several centimeters intra-abdominally. During the creation of the additional length, the gastric lumen is not entered, and leakage with its attendant morbidity and mortality is obviated.

Long term studies up to three years with fiberoptic photography, esophagrams, and intraluminal pressure studies have confirmed the soundness of the experimental procedure.

Recent clinical experiences have encouraged us to regard the procedure as applicable and curative. The first patient has had no dysphagia or recurrence of her esophageal hemorrhage. Postoperative fiberesophagoscopy has revealed complete healing of the lower esophageal erosions. The other two patients have remained asymptomatic for many months. We will continue to follow these cases for long term results.

Acknowledgment

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Femoroperoneal Bypass:

Evaluation of Potential for Revascularization of the Severely Ischemic Lower Extremity

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In 79 patients in whom distal small vessel bypass with autogenous vein was used for revascularization because of gangrene, gangrenous ulceration or rest pain, 14 had femoroperoneal bypasses. Femorotibial or femoroperoneal bypasses were performed in those patients in whom no popliteal runoff was present on pre-operative arteriogram. Femoroperoneal bypass was performed in preference to primary amputation in each case. Nine of 14 (64.3%) of femoroperoneal bypasses were functional whereas 57 of 79 (72.2%) of total distal bypasses to small vessels were functional. Salvage of severely ischemic lower extremities was achieved in 5 of 14 (35.7%) patients after femoroperoneal bypass and in 46 of 65 (70.8%) patients after bypass to anterior tibial or posterior tibial arteries. Graft patency without limb salvage occurred in 4 of 9 (44.4%) patients with patent femoroperoneal bypasses and in only 2 of 48 (4.2%) of patients with femorotibial bypass. Although limb salvage rate is considerably less with femoroperoneal than femorotibial or femoropopliteal bypass, attempted limb revascularization by peroneal bypasses is preferable to primary amputation in patients with rest pain, gangrenous ulceration or gangrene.

EXPERIENCE with long autogenous saphenous vein bypasses to the small arteries of the severely ichemic lower extremity distal to the popliteal has been reported.[1-4] Limb salvage after distal small vessel bypass in 79 patients operated for gangrene, gangrenous ulceration or rest pain is 64.6%.[4] Long-term limb salvage results in most patients in whom initial limb salvage is achieved.[3] Most bypasses to the distal lower extremity are femorotibial. Little experience has been reported with bypasses to the peroneal artery. Of the 79 patients without popliteal run-off, 14 had only peroneal artery visualized on preoperative angiogram. In these patients femoroperoneal bypass was performed in preference to primary amputation in each case.

Methods

Either continuous epidural or general anesthesia was used. Because 2–4 hours of operating time are required, regional anesthesia is preferred when possible. A medial incision is used to approach the peroneal artery. The incision parallels the posterior aspect of the tibia and is carried through the tibial attachment of the soleus muscle. In approaching the peroneal artery, the posterior tibial artery is encountered first in a fascial plane deep to the soleus muscle. The peroneal vessels are located more laterally and in the same fascial plane. In its more distal course, the peroneal vessel may enter the substance of the flexor hallucis longus muscle and may therefore be difficult to find. The peroneal artery is explored before femoral artery dissection, to first determine the pliability of the artery. If the artery is deemed suitable on the basis of external operative inspection, arteriotomy is performed and run-off is assessed in both cephalad and caudad directions. Heparinized saline solution is instilled into the proximal and distal vessel shortly after the arteriotomy is performed to prevent intraarterial thrombosis, and to assess ease of injection in both directions. Low grade magnification is used as previously described.[4]

All bypasses were performed with reversed autogenous saphenous vein graft except in one patient in whom the

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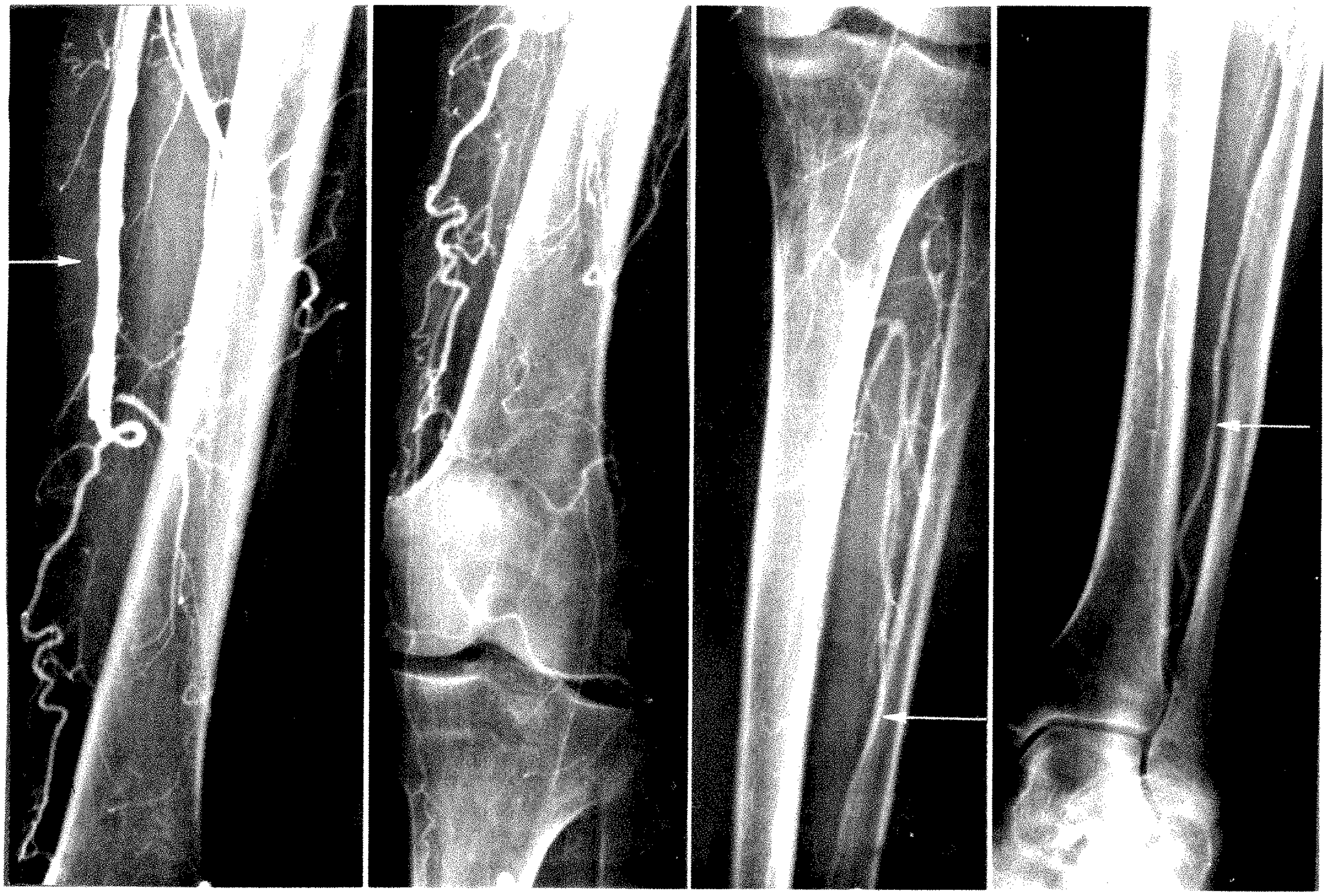
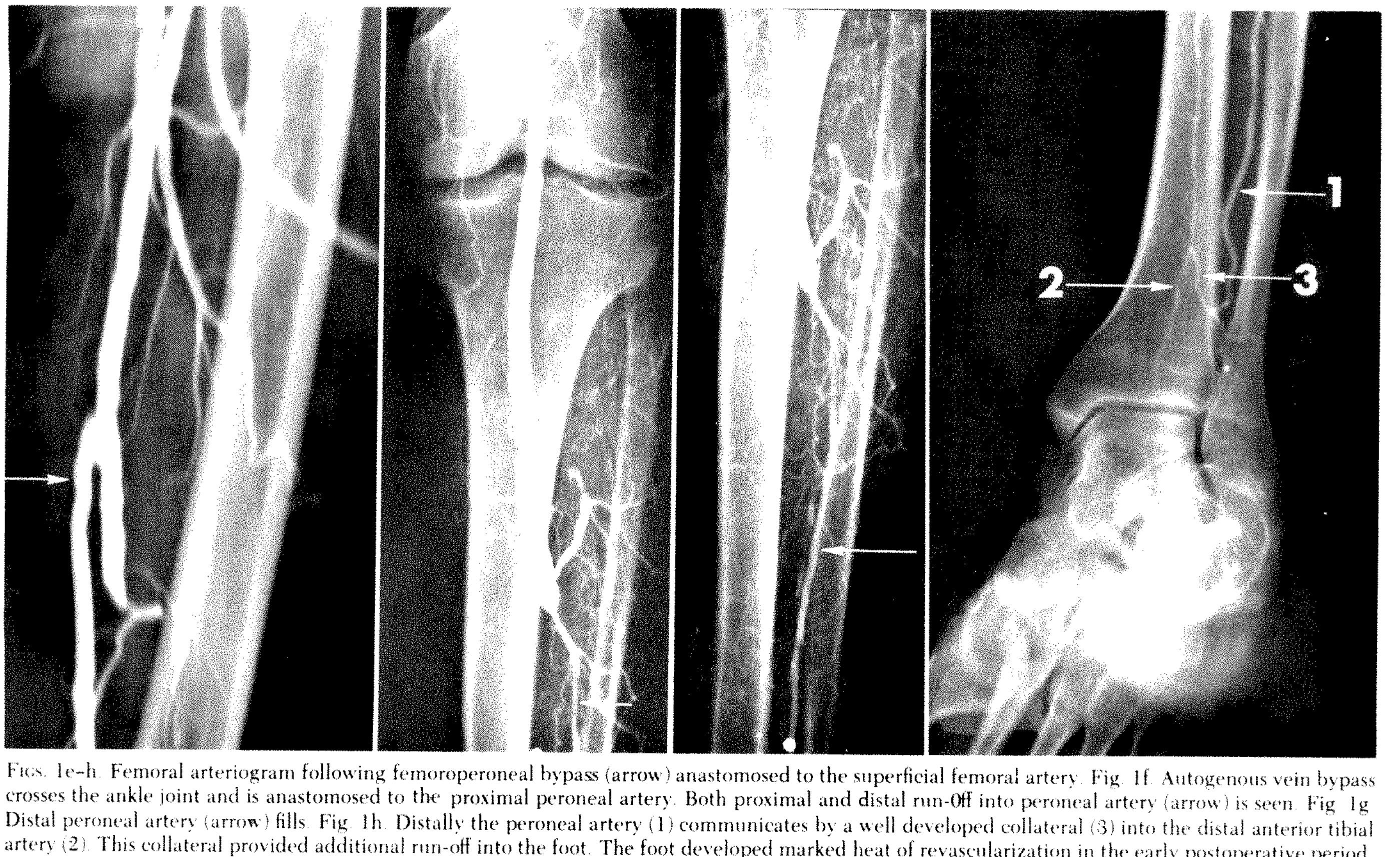
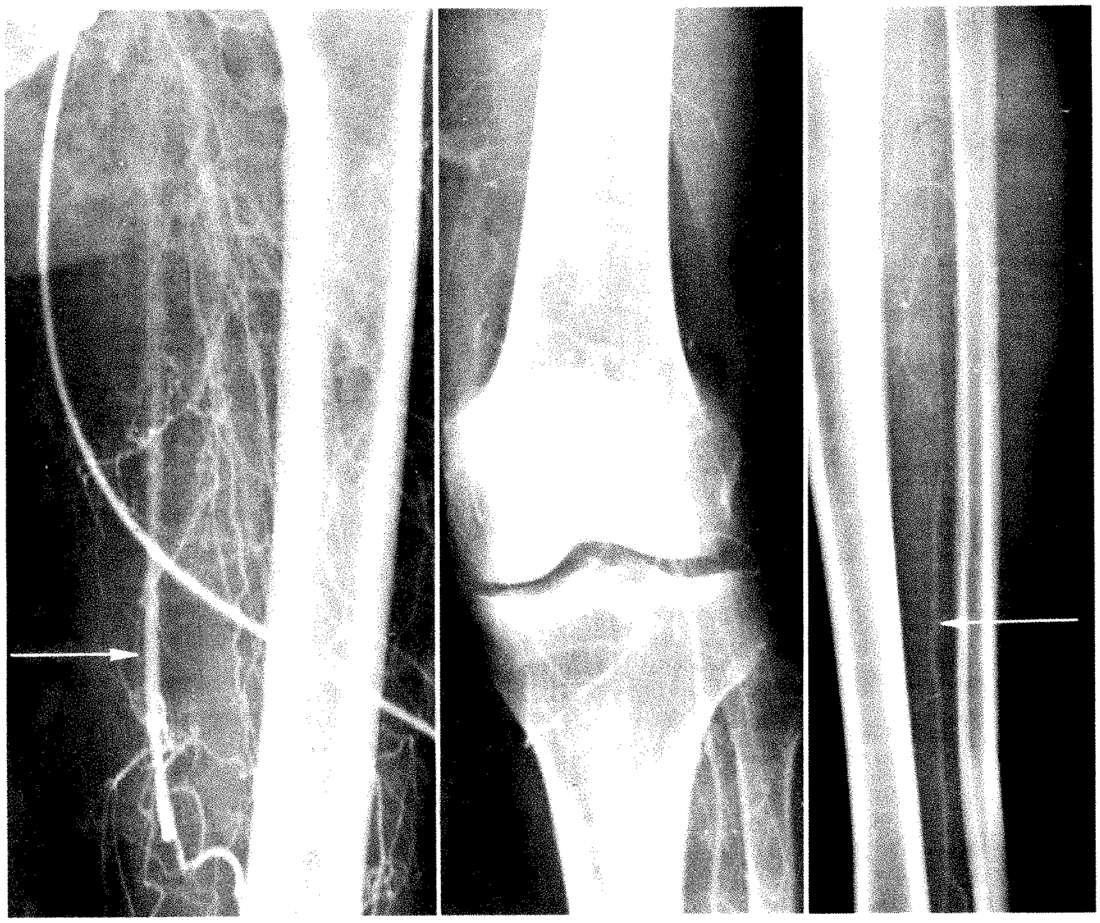


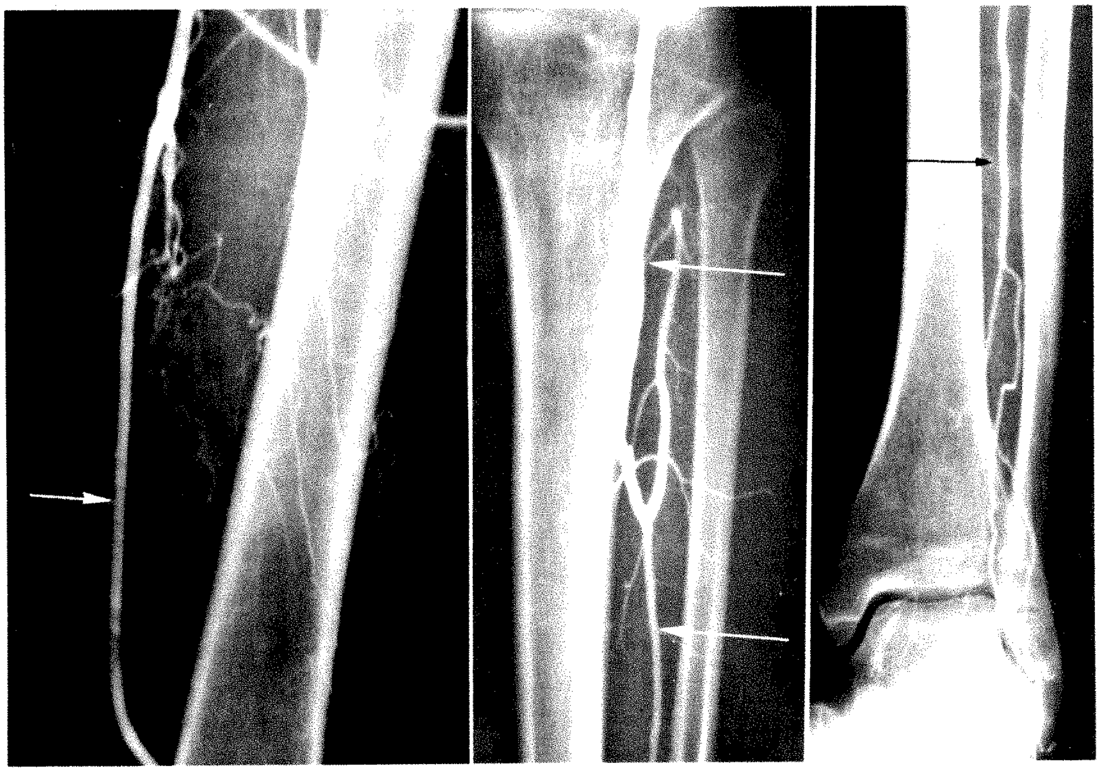
Figs. 1a–d. Preoperative angiogram of a 58-year-old male who had rest pain of the left lower extremity. (From left to right) Fig. 1a. Occlusion of the mid-superficial femoral artery. Fig. 1b. Absent popliteal run-off is observed despite collaterals visualized in the region of the popliteal space (arrow). Figs. 1c and 1d. The peroneal artery (arrows) is visualized along its entire length to the ankle.



Figs. 1e–h. Femoral arteriogram following femoroperoneal bypass (arrow) anastomosed to the superficial femoral artery. Fig. 1f. Autogenous vein bypass crosses the ankle joint and is anastomosed to the proximal peroneal artery. Both proximal and distal run-Off into peroneal artery (arrow) is seen. Fig. 1g. Distal peroneal artery (arrow) fills. Fig. 1h. Distally the peroneal artery (1) communicates by a well developed collateral (3) into the distal anterior tibial artery (2). This collateral provided additional run-off into the foot. The foot developed marked heat of revascularization in the early postoperative period. The patient gradually developed a dorsalis pedis pulse which gradually increased in amplitude in the postoperative period.



Figs. 2a–c. Preoperative femoral arteriogram in a 55-year-old physician with rest pain and digital ulceration of the left lower extremity. (Left to right) Fig. 2a. Occlusion of the superficial femoral artery (arrow). Fig. 2b. Absent popliteal run-off despite collaterals which are visualized in the popliteal area. Fig. 2c. Peroneal artery (arrow) is the only vessel visualized in the distal extremity on preoperative angiogram.



Figs. 2d–f. Femoral arteriogram after femoroperoneal bypass. This bypass has functioned for 69 months. The patient is still active and asymptomatic. (Left to right) Fig. 2d. Autogenous saphenous vein bypass (arrow) originating from the superficial femoral artery. Fig. 2e. Autogenous vein bypass (arrow) anastomosed end-to-side into the peroneal artery (arrow). Fig. 2f. Distal peroneal artery (arrow) with run-off into the foot. Anastomosis of unnamed collaterals around the lateral aspect of the ankle and foot. Long-term graft function and limb salvage may be related to the abundance of distal collaterals. No dorsalis pedis or posterior tibial filling in the foot can be demonstrated.

TABLE 1. *Incidence of Functional Bypasses*

Type Bypass	Incidence of Bypass Function
Femoroperoneal	9/14 (63.4%)
Femorotibial	48/65 (73.8%)
Total Small Vessel	57/79 (72.2%)

saphenous vein was inadequate. In this patient an 8 mm Dacron prosthesis was anastomosed into the proximal peroneal artery. However, the bypass immediately thrombosed and was unsuccessful.

Angiographic demonstration of a patent distal vessel with an adequate arteriogram is essential in selection of patients for bypass. Demonstration of collateral vessels in the region of the non-visualized main distal artery is considered evidence of an adequate arteriogram.

Results

Nine of the 14 (63.4%) of the femoroperoneal bypasses were functional (Table 1). This is only slightly less than the incidence of functional bypasses in our total series in which 57 of 79 (72.2%) bypasses to small vessels distal to the popliteal were functional. Similarly, 48 of 65 (73.8%) femorotibial bypasses were functional.

However, graft patency without limb salvage occurred in 4 of 9 (44.4%) patients with patent femoroperoneal bypasses (Table 2). In contrast graft patency without limb salvage occurred in only 2 of 48 (4.2%) of patients with femorotibial bypass. Salvage of severely ischemic lower extremities was achieved in 5 of 14 (35.7%) patients after femoroperoneal bypass and in 46 of 65 (70.8%) patients after femorotibial bypass (Table 3). Over-all limb salvage following femorotibial or femoroperoneal bypass occurred in 51 of 79 (64.6%) patients (Table 3) (1).

Of the 5 patients achieving limb salvage after femoroperoneal bypass two patients are presently alive with functional bypasses. The average duration of patent bypass with limb salvage in these patients is now 54.5 months. Three patients died with patent femoroperoneal bypasses and had limb salvage until the time of death. The average duration of graft patency with limb salvage at the time of death of these three patients was 29.3 months. Overall average duration of graft patency in the five patients achieving limb salvage is 34.4 months at the present time. The patient with the longest patent bypass and limb salvage is now 69 months following bypass (Fig. 1). He is entirely asymptomatic and quite active. No late bypass occlusions have occurred in any patients who had femoroperoneal bypass resulting in patent bypass and initial limb salvage.

TABLE 2. *Graft Patency without Limb Salvage*

Femorotibial Bypass	2/48 (4.2%)
Femoroperoneal Bypass	4/9 (44.4%)

TABLE 3. *Limb Salvage after Small Vessel Bypass*

Femoroperoneal	5/14 (35.7%)
Femorotibial	46/65 (70.8%)
Total Small Vessel	51/79 (64.6%)

Ten of the 14 (71.4%) patients in whom femoroperoneal bypass was performed were diabetic (Table 4). By comparison 31 of 65 (47.7%) patients who had femorotibial bypass had diabetes. No postoperative mortality occurred after femoroperoneal bypass.

TABLE 4. *Incidence of Diabetes Mellitus in Patients Bypassed*

Femoroperoneal	10/14 (71.4%)
Femorotibial	31/65 (47.7%)

Discussion

In assessing the value of femoroperoneal bypass, consideration of the preoperative indications is of prime importance. Patients in this series were operated on primarily for limb salvage. Bypasses were performed in lieu of primary amputation. Preoperative indications included gangrene, gangrenous ulceration and rest pain. No patients undergoing femoroperoneal bypass had intermittent claudication as the only operative indication. As a salvage procedure, even 35% limb salvage would seem satisfactory. On the basis of these results, femoroperoneal bypass is not indicated for claudication alone unless the claudication interferes with the patient's occupation.

Bypass function without limb salvage is considerably more common after bypass to the peroneal artery than after bypass to anterior or posterior tibial arteries. This is presumably related to the anatomic distribution of the peroneal artery which frequently has little distal run-off into the foot. In some patients, however, extensive run-off through collaterals may contribute to continued patency of femoroperoneal bypasses and revascularization of distal ischemic tissues (Figs. 1a–h and 2a–f).

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Effect of Complete Parenteral Nutrition Using Fat Emulsion on Liver

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Four to 8 weeks of complete parenteral nutrition including fat emulsion, 10% Intralipid, from 2 to 4 gm/kg/day, was studied in puppies. The following conclusions were reached: At the end of 4–8 weeks of complete parenteral nutrition using the infusion of fat emulsion, the lipid content of the liver was twice the value in control animals, which returned to the approximate normal value in a short period after the interruption of the fat emulsion. This increase in the lipid content was considered to be caused by a proper metabolic process of fat emulsion and would seem to indicate that the daily infusion of the fat emulsion from 2 to 4 gm could be performed safely for an extended period of time.

HYPERALIMENTATION and complete parenteral nutrition are often used in pediatric surgery. For many reasons, fat emulsion is necessary in order to obtain the required intravenous supply of energy in such cases. This study was designed to determine the effect of the prolonged infusion of fat emulsion on the liver of immature dogs who were maintained on a complete parenteral nutrition, including "Intralipid" for 4 to 8 weeks.

Materials and Methods

Seven, two or three-member litters of puppies, or a total of 17 animals, 8–10 weeks old were used. A silicone rubber catheter was inserted into an external jugular vein and threaded into the superior vena cava of one or two animals of each litter.[5] The animals were sustained exclusively by vein receiving 140 Cal/kg of body wt/day. The solution, infused over a 21–23 hour period daily, consisted of 4 gm of amino acid mixtures/kg of body weight, carbohydrate, fat and all the vitamins and minerals recommended for growth in dogs (Table 1).[5] The provision of carbohydrate varied according to the fat intake. The experimental animals were divided into three groups. Group 1: two animals (4 week experiment) received 2 gm of fat/kg/day. Group 2: three animals (4 week experiment) received 3 gm of fat/kg/day. Group 3: three animals (4 week experiment) and two (8 week experiment) received 4 gm of fat/kg/day. Ten per cent Intralipid[°] was used as the fat emulsion (Table 2). It was infused over an 8–10 hour period in each 24 hours with 8 u of heparin/kg of body wt/hr. Complete parenteral nutrition, with 31 gm of carbohydrate and 4 gm of amino acid mixtures/kg of body weight was continued after the 4 week experiment for 5 days in one animal (dog 36, Group 2) and for 10 days in a second animal (dog 44, Group 3). The litter mate controls (seven animals) were fed Clea dog food (commercial food with an adequate content of calories, minerals and vitamines) at the same caloric levels as the experimental animals. The average daily fat intake was 3.5 gm/kg of body weight. During the experiment using the fat emulsion, blood samples were taken at 2 week intervals in both the experimental and the control animals. In dogs 36 and 44, the blood was drawn after 5 and 10 days respectively, on a fat free solution. The concentrations of plasma lipids, electrophoretic analysis of plasma by the method of Noble,[12] the fatty acid composition of the plasma lipids, serum GOT and GPT, and other various determinations were carried out on each blood sample.[11] The animals were sacrificed by exsanguination, 12–14 hours after the completion of the last fat emulsion in the experimental animals excluding dogs 36 and 44, which were sacrificed in the same manner after 5 and 10 days respectively on a fat free solution. The control animals were sacrificed after overnight

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TABLE 1. *Composition of the Intravenous Diet*

Nutrients (/kg/day)		Vitamins (/kg/day)		Minerals (mg/kg/day)	
Protein	4.0 gm	A	1,000 I.U.	Calcium	72
Carbohydrate	22–31 gm	D	100 I.U.	Phosphorus	96
Fat	2–4 gm	E	0.51 I.U.	Sodium	120
Calories	140 Cal	Choline	25 mg	Potassium	170
Water	140–190 ml	B_{12}	0.003 mg	Chloride	315
		Folic Acid	0.015 mg	Magnesium	20
		Thiamine	5.0 mg	Copper	0.1
		Riboflavin	1.0 mg	Cobalt	0.05
		Pyridoxine	1.5 mg	Manganese	0.2
		Pantothenic acid	2.5 mg	Zinc	0.2
		Niacin	1.0 mg	Iodine	0.06
		K	0.1 mg	Iron	1.0
		Biotin	0.007 mg		
		PABA	2.0 mg		

fast. At the time of necropsy, livers were removed and were fixed in 10% neutral buffered formalin. Tissue specimens from livers were frozen and stored at − 20 C for biochemical studies. Tissue specimens were subjected to various histopathological procedures, and those histochemical procedures characterizing "intravenous fat pigment."[13] Hepatic lipids were extracted,[8] evaporated to dryness and determined as "total lipids" by weight. The lipid fractions were separated by thin-layer chromatography on silica gel G, and the quantitative determinations were performed by the following methods: Lipid phosphorus, method of Bauman.[3] Total cholesterol, method of Zurkowski;[16] Triglycerides, method of Fletcher;[7] Nonesterified fatty acids (NEFA), method of Duncombe.[6] The fatty acid composition of the hepatic lipids was determined by gas-liquid chromatography.

Results

1. *Liver, Spleen and Lung Weight*

There were no remarkable changes in the liver, spleen and lung weight, calculated per gram weight.

TABLE 2. A. *Lipid Composition of Intralipid and Clea Dog Food*

	Intralipid (gm/100 ml)	Clea Dog Food (gm/100 gm)
Triglycerides	9.79	3.35
NEFA	0.11	0.53
Lipid phosphorus	0.04	0.01
Cholesterol	0.06	0.02

B. *Fatty Acid Composition (wt. %) of Intralipid and of Triglycerides of Intralipid and Clea Dog Food*

Fatty Acid	Intralipid	Triglycerides of Intralipid	Triglycerides of Clea dog food
C16 = 0	11.6	11.2	20.4
C16 = 1	0.4	1.1	2.5
C18 = 0	3.8	3.2	11.1
C18 = 1	26.6	27.6	36.3
C18 = 2	50.0	49.4	25.2
Others	7.6	7.5	4.2

2. *Histopathological Studies*

The experimental animals showed a slight accumulation of fat in the parenchymatous cells of the liver, and the proliferation of and the accumulation of fat in reticuloendothelial cells of the liver, spleen and lung. "Intravenous fat pigment" in Kupffer cells and the accumulation of reticuloendothelial cells with "intravenous fat pigment" were demonstrated in the liver. No other pathological changes were defined microscopically in the tissue specimens collected from major organs.

3. *Hepatic Lipid*

(a) Total Lipid (Fig. 1). The three experimental animals averaged twofold increases in the total lipid content. In dogs 36 and 44, the total lipid content returned to approximately the control value.

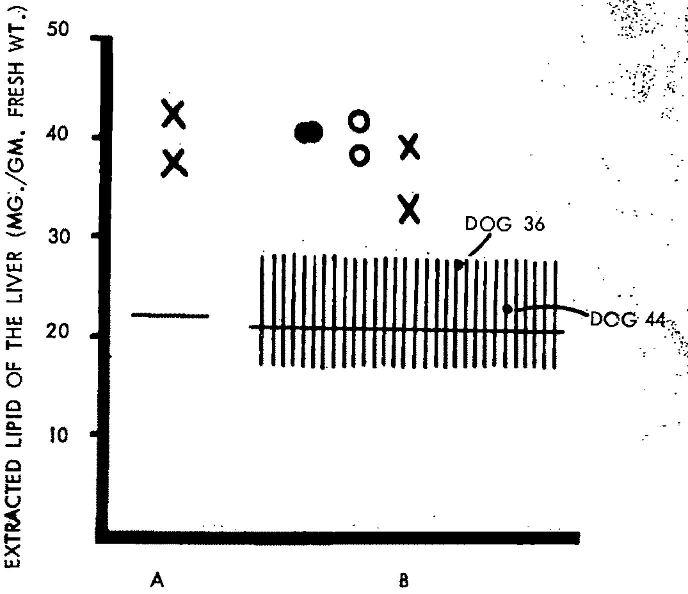

FIG. 1. Effect of complete parenteral nutrition including fat emulsion on the extracted lipid of the liver (total lipid). "A" represents the result of the 8-week experiment. "B" represents the results of the 4-week experiment. ● Group 1. ○ Group 2. × Group 3. ++++ Control group (the mean value and the range of the value).

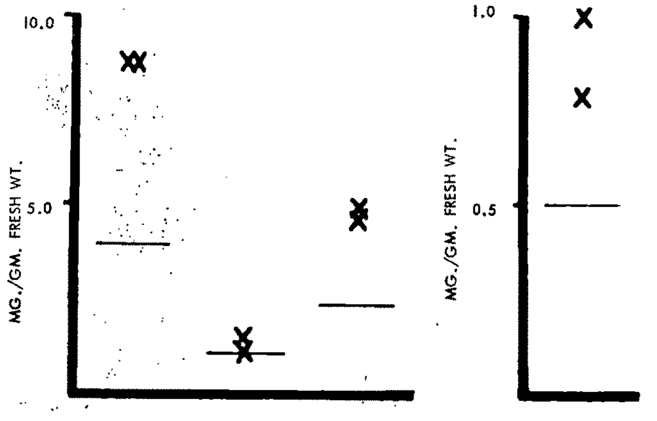

FIG. 2. Effect of complete parenteral nutrition including fat emulsion on the hepatic lipid fractions in the 8-week experiment. × Group 3. ——— Control Group.

(b) Hepatic Lipid Fractions (Figs. 2 and 3). In the 4 and 8 week experimental animals there was a marked increase in hepatic lipid fractions. There were twofold increases in the lipid phosphorus, cholesterol and NEFA contents and a slight increase in the triglyceride content. In dogs 36 and 44, the hepatic cholesterol content was below the control value, and the lipid phosphorus and NEFA contents were approximately the control value. The triglyceride content was slightly higher than that of the control group.

(c) Fatty Acid Composition of the Hepatic Lipid Fractions (Fig. 4). In the experimental animals, the fatty acid composition of hepatic phospholipids differed from that of the fat emulsion and of its phospholipid component.

In the 4 and 8 week experimental animals, the fatty acid composition of the cholesterol esters differed from that of the fat emulsion, and of dogs 36 and 44. However, it had considerable similarity to the fatty acid composition of the fat emulsion as a whole.

There was remarkable similarity in the fatty acid composition of the hepatic triglyceride fraction of the 4 and 8 week experimental animals, that of triglyceride component of the fat emulsion and of the fat emulsion as a whole. Dogs 36 and 44, differed in their patterns of acids from other experimental animals.

4. Plasma Lipids[11]

Two to threefold increases in the plasma lipid phosphorus, cholesterol and triglyceride levels were detected throughout the 4–8 weeks of the infusion of fat emulsion and those increased plasma lipid fractions were proven to be of endogenous origin. After 5 and 10 days on a fat-free solution, the levels of plasma lipid fractions of dogs 36 and 44 decreased to approximately the initial values. The fatty acid composition of plasma lipid fractions was similar to that of hepatic lipid fractions. Lipoprotein electrophoresis on agarose gel disclosed that α and β-lipoproteins increased in the experimental animals during the 4 and 8 weeks of the infusion of the fat emulsion.

5. Serum GOT and GPT

There was no significant deviation from the normal in serum GOT and GPT.

Slight ketonemias were observed during the 4 and 8 weeks of the infusion of the fat emulsion. There were no remarkable changes in blood sugar, venous blood pH or in other various determinations. The animals were in good condition. In both the experimental and the control animals, their growth, development and weight gains were observed to be approximately normal.

Discussion

Because Intralipid consists of triglycerides, phospholipids, cholesterol and NEFA, it would seem important to investigate whether the increased hepatic fractions

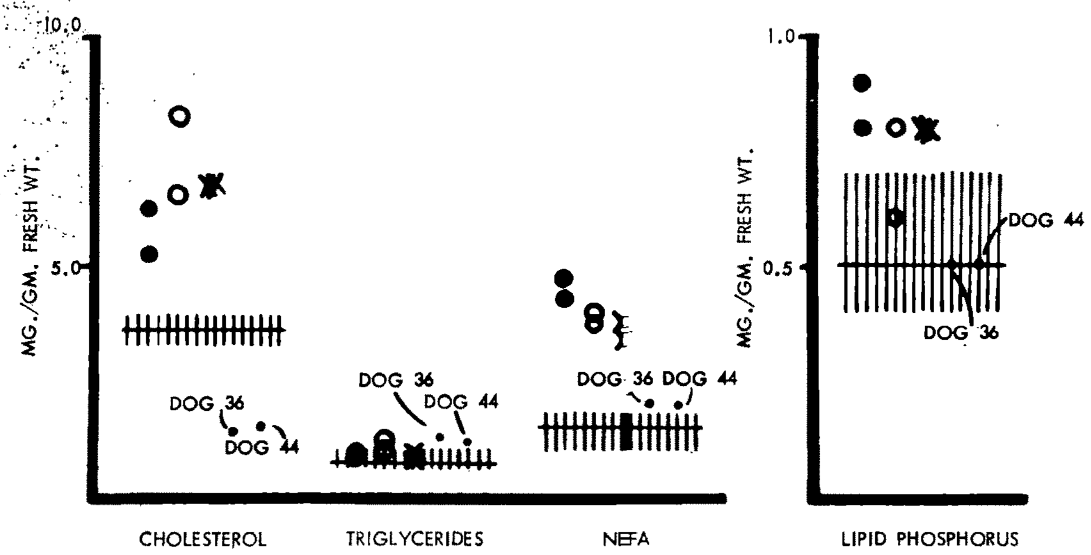

FIG. 3. Effect of complete parenteral nutrition including fat emulsion on the hepatic lipid fractions in the 4-week experiment. ● Group 1. ○ Group 2. × Group 3. ┼┼┼┼┼┼┼ Control group (the mean value and the range of the value).

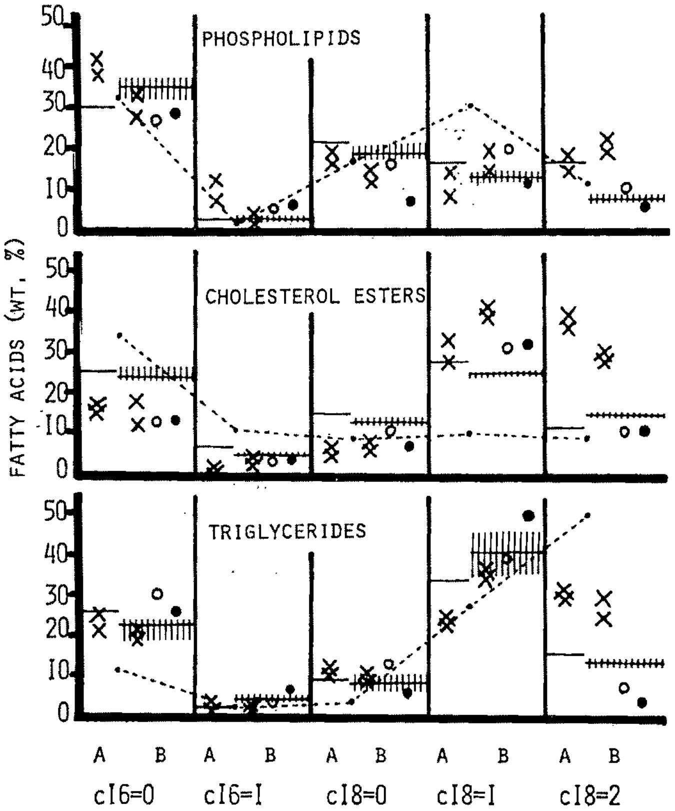

FIG. 4. Changes in the fatty acid composition (wt. %) of liver phospholipids, cholesterol esters and triglycerides in the 4 to 8-week complete parenteral nutrition. "A" represents the result of the 8-week experiment. "B" represents the results of the 4-week experiment and of dogs 36 and 44 after 5 and 10 days, respectively, on a fat-free solution after 4 weeks. ○ dog 36. ● dog 44. ┼┼┼┼┼ Control group (the mean value and the range of the value)----- Intralipid.

were of exogenous origin, *i.e.*, they were the accumulation of the fat emulsion in the liver, or were of endogenous origin. To determine this, the fatty acid composition of the hepatic lipid fractions were examined. Because of the extremely short half life of NEFA,[14] the NEFA of the infused fat emulsion might be metabolized rapidly and those in the liver were assumed to be endogenous. It was found that the fatty acid composition of phospholipid component of the fat emulsion and the hepatic lipids were dissimilar as were those of cholesterol esters in the fat emulsion and the hepatic lipids. The fatty acid composition of the hepatic triglycerides had striking similarity to that of the fat emulsion as a whole. In this experiment, the plasma triglycerides whose fatty acid composition was similar to that of the fat emulsion as a whole were proven to be endogenous.[11] There is experimental evidence that the acid mixtures of the triglycerides were altered by the dietary fats.[1] Therefore, in the case of the intravenous fat administration, the same phenomenon might apply to the hepatic triglycerides. Thus, the evidence has been obtained that the increased hepatic lipid fractions might come from endogenous synthesis.

In this experiment, the three experimental animals averaged twofold increases in the total hepatic lipids and in hepatic lipid fractions, regardless of the length of the total infusion period and the daily volume of the fat emulsion administered. Those changes in the hepatic lipids, however, diminished and returned to nearly the initial values shortly after the interruption of the fat emulsion as noted in dogs 36 and 44.

It is worthy of note that the long-term daily fat emulsion, largely composed of triglycerides, led to marked rises in the hepatic phospholipid and cholesterol contents as well as in the triglyceride content; and the increases in the former were more prominent. The constituent of the fat emulsion might be reformed into other esters within the liver and reenter the blood stream as lipoproteins. In this experiment, α and β-lipoproteins, reportedly rich in cholesterol and phospholipids,[10] seemed to perform the major lipid transport tasks in the experimental animals. What is actually responsible for the increase in the hepatic lipids, particularly with phospholipids and cholesterol is not completely understood; however, enhanced endogenous synthesis of α and β-lipoproteins in the liver, appears to have an important role. Evidence for this view is based on our observations that in the 4 and 8 week experimental animals, plasma lipid fractions, proved to be largely endogenous, were also elevated, concomitant with the rise in α and β-lipoproteins in the circulation.[11] The infused fat emulsion might lead to the enhancement in lipid transport tasks for final uptake by the utilizing tissues. α and β-lipoproteins seemed to be produced vigorously for this purpose, and the cholesterol and phospholipids might be demanded as structural components of lipoproteins.[9] Because there is abundant evidence that the liver is the chief source of the circulating lipoproteins and lipids derived from endogenous synthesis,[2] vigorous production of α and β-lipoproteins might cause the enhanced production of and the increase in phospholipids and cholesterol in the liver. Although in this experiment the experimental and the control animals received approximately the same amount of fat, the lipid content of the liver was markedly increased when the experimental animals were compared with the control animals. This might be due to the differences in the metabolic pathway between the fat given orally and intravenously.[4] Five and 10 days after the completion of the last fat emulsion, however, those changes in the hepatic lipids returned to approximately the control values and the fatty acid composition of the hepatic cholesterol esters and triglycerides showed different results from those obtained at the end of 4 and 8 weeks of infusion of the fat emulsion. The phospholipids appeared to be influenced little in their fatty acid composition by the fat emulsion, as in the case of dietary fat.[1] These phenomenon were presumed to indicate that the enhanced lipid metabolism, because of the fat emulsion, returned approximately to its initial level in 5–10 days after its interruption, exerting no residual ill effect. Furthermore, it was obtained that the animals remained in good condition, and their growth, development, and weight gain were observed to be approximately normal. Thus, daily infusion of fat emulsion, from 2 to 4 gm/kg of body weight could be performed safely for an extended period.

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Effect of Antrectomy and Subsequent Vagotomy on the Serum Gastrin Response to Food in Dogs

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The effect of food on serum gastrin and gastric acid secretion has been studied in dogs with denervated pouches before and after antrectomy and subsequent vagotomy. A Billroth I anastomosis was used in one group of dogs and a Billroth II in the other. Serum gastrin was measured by radioimmunoassay. In both groups of dogs antrectomy significantly depressed mean basal levels of serum gastrin and abolished the rise in serum gastrin in response to a meat meal. Meal-induced pouch acid secretion was considerably lowered by antrectomy after either Billroth I or Billroth II anastomosis. Vagotomy after antrectomy increased basal levels of gastrin, but did not restore the serum gastrin response to a meat meal in either group of dogs. It is suggested that biologically active forms of gastrin are released from the antrum in response to a meal. Biologically inactive basal levels of gastrin apparently originate from extra-antral sources. The post-vagotomy increase in basal (static) gastrin suggests vagal control of the metabolism of static, extra-antral gastrin.

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Appreciable quantities of extra-antral gastrin within the gastrointestinal tract of man and animals have been demonstrated by radioimmunoassay[3,6,15,21,25] and by immunohistochemical techniques.[8,12] The effect of food, the ordinary physiological stimulus, upon stores of extra-antral gastrin is not completely understood. In man after gastrectomy,[10] antrectomy,[10] or antrectomy and vagotomy,[1,10,18] feeding continues to elicit an increase in the serum concentration of gastrin apparently as a consequence of the release of extra-antral gastrin. We have demonstrated[14] only minute rises in serum gastrin after feeding in dogs after gastrectomy. This suggests an important difference in the availability of extra-antral gastrin of the dog compared with man. The effects of antrectomy alone on the serum gastrin response to food in dogs are unknown.

The present experiments were undertaken to study further the release of extra-antral gastrin stimulated by food in dogs.

Materials and Methods

Twelve healthy adult mongrel dogs, 15–25 kg, with denervated fundic Heidenhain pouches (HP) were studied. Serum gastrin concentrations and HP acid secretion were measured in response to a standard meat meal before and 3 weeks after antrectomy.

Each dog underwent an 18 hour fast after which a catheter was placed in a hindleg vein for sampling. Duplicate basal blood samples were drawn for serum gastrin determination and two basal 15-minute HP collections were made. The dogs were then fed a 200 gm meat meal. Blood samples were drawn at frequent intervals and HP collections were made every 15 minutes during the subsequent 3 hours.

The dogs were then subjected to antrectomy under sodium pentothal anesthesia. The antrum was defined in each dog at laparotomy. A distal gastrotomy was performed and the acid-secreting area of the stomach was outlined with pH paper 15 minutes after the subcutaneous injection of 50 mg of Histalog. The entire antrum was excised, along with a 1 cm margin of acid-secreting mucosa. The distal line of resection was the pylorus. Dogs were randomly divided into two groups; in one group, gastrointestinal continuity was restored by means of a Billroth I gastroduodenal anastomosis, and in the second group a Billroth II gastrojejunostomy was performed. Three weeks after antrectomy, food studies were repeated.

Three to five days after the food studies, four of the dogs with a Billroth I anastomosis and five of the Billroth II dogs were again anesthetized and underwent bilateral truncal

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vagotomy. Three weeks later, food studies were again repeated.

To secure more information on the effect of antrectomy and vagotomy on *basal* gastrin, four additional blood samples were taken from each dog preoperatively, after antrectomy and after vagotomy.

Acid output, expressed as milliequivalents (mEq)/15 minutes, was calculated by measuring the amount of acid in a 1 ml aliquot of HP secretion which was titrated with 0.1 N NaOH, using phenol red as indicator.

Serum gastrin was measured by radioimmunoassay[9] The antigastrin antibody used was developed in rabbits to synthetic human gastrin I (amino acid residues 2–17 conjugated to bovine serum albumin. All samples were assayed in duplicate; reproducibility was within ±10%. The average of the duplicates was used. Gastrin concentrations are expressed in picograms (pg)/ml. Integrated gastrin responses to food were calculated from the product of the mean serum gastrin level during each time period after feeding multiplied times the number of minutes in the study minus the product of mean *basal* gastrin level and the number in minutes.[20] Integrated gastrin was expressed as ng-min/ml for the time period. Results were expressed as arithmetic means and standard errors of the mean. Student's "t" test was used to determine significance of differences between means. Differences with *p* values less than 0.05 were considered significant.

Results

Serum gastrin levels and HP secretory responses to food before and after antrectomy with Billroth I anastomosis are shown in Fig. 1. Basal serum gastrin was 69 ± 4 pg/ml before antrectomy and 62 ± 3 pg/ml after antrectomy ($p > 0.05$). Before antrectomy, serum gastrin rose significantly after food to a peak of 146 ± 10 pg/ml ($p < 0.05$) at 15 minutes and remained elevated. After antrectomy, there was no significant increase in serum gastrin values after food.

Pouch acid secretion before antrectomy rose at 105 minutes to a peak of 0.54 ± 0.15 mEq/15 minutes in response to food. After antrectomy, the HP response was diminished; the differences were significant ($p < 0.05$) at all except the first collection period.

Results of serum gastrin and HP acid measurements before and after antrectomy with Billroth II anastomosis are shown in Fig. 2. Before antrectomy, the basal concentration of serum gastrin was 79 ± 9 pg/ml; the value was significantly lower after antrectomy (55 ± 2 pg/ml, $p < 0.05$). Prior to antrectomy, serum gastrin after food rose to a peak of 120 ± 11 pg/ml and remained elevated. After antrectomy, feeding produced no significant alteration of basal levels of serum gastrin. If basal values are different, the post-prandial gastrin levels are best compared by an evaluation of the integrated gastrin response.[20] The 180-minute integrated gastrin response was 3.94 ± 1.42 ng-min/ml before antrectomy and 1.39 ± 0.74 ng-min/ml after antrectomy ($p < 0.05$).

HP acid secretion before antrectomy rose to a peak of 0.51 ± 0.19 mEq/15 minutes after feeding (Fig. 2). After antrectomy HP acid secretion was significantly diminished ($p < 0.05$). During the third hour after feeding, acid output increased, but the response remained significantly lower than prior to antrectomy.

After vagotomy basal serum gastrin was 83 ± 15 pg/ml with Billroth I anastomosis and 79 ± 8 pg/ml with Billroth II anastomosis (Fig. 3). There was no significant alteration in serum gastrin in response to food in either group. HP acid responses to food in both Billroth I and Billroth II dogs were not significantly altered by the addition of vagotomy.

In the additional study on the effect of antrectomy and vagotomy on *basal* gastrin, the average of four basal gastrin values in the Billroth I group was 71 ± 3 pg/ml before antrectomy and 59 ± 2 pg/ml after antrectomy ($p < 0.05$). In the Billroth II dogs, the pre-antrectomy gastrin values were 74 ± 4 pg/ml. After antrectomy, the average levels were 56 ± 2 pg/ml ($p < 0.05$). After vagotomy, serum gastrin levels were 89 ± 7 pg/ml in Billroth I dogs and 85 ± 4 pg/ml in Billroth II; both levels were higher ($p < 0.01$ for both groups) than after antrectomy alone.

Discussion

These results demonstrate that antrectomy diminished basal concentrations of gastrin, abolished the post-prandial rise in serum gastrin and considerably diminished gastric acid secretion in response to a meat meal. When vagotomy was added to antrectomy, basal gastrin was significantly increased, but the previous abolition of the gastrin response to a meal and the diminished HP acid response to food were unchanged.

Although antrectomy significantly depressed basal levels of serum gastrin it did not abolish them, suggesting that sites of extra-antral gastrin were present and were actively producing gastrin. Since antrectomy abolished the post-prandial rise of gastrin (kinetic gastrin) but decreased only slightly the basal levels (static gastrin), it may be that the antrum is chiefly responsible for kinetic gastrin (that is, gastrin released in response to food) and the small bowel for static (or basal) gastrin. Yalow and Wu[27] found that big big gastrin was a major component of unstimulated (static) gastrin, and Yalow[26] found that big big gastrin was not released by feeding. It may be that in dogs at least, the antrum contributes the major component of kinetic, biologically active gastrin (presumably 17-amino acid and 34-amino acid gastrin) and the small intestine may be chiefly responsible for basal, non-biologically active levels (presumably chiefly big big gastrin[27]. The rise in basal gastrin after vagotomy suggests that the vagus influences mechanisms for the release or catabolism of extra-antral gastrin.

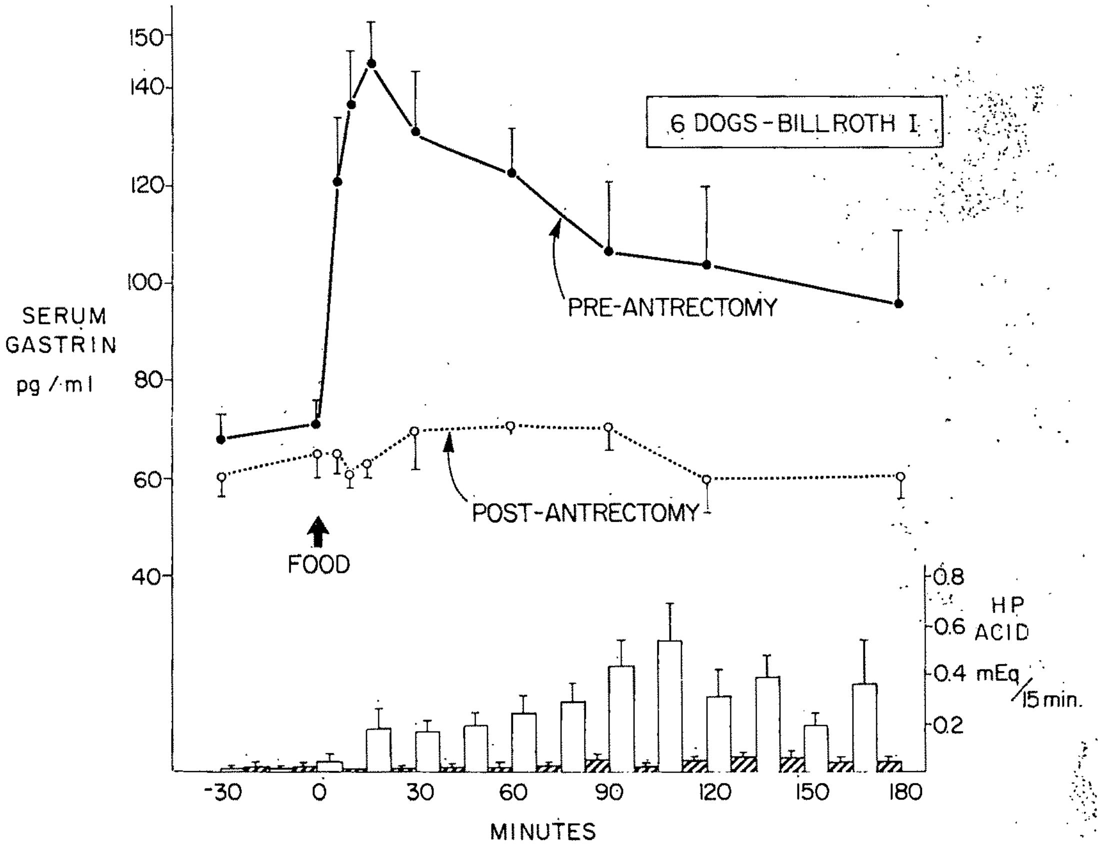

Fig. 1. Basal and postprandial serum gastrin and Heidenhain pouch acid values in six dogs before and after antrectomy with gastroduodenostomy (Billroth I). Pre-antrectomy acid values are shown by the open bars and post-antrectomy values are shown by the striped bars.

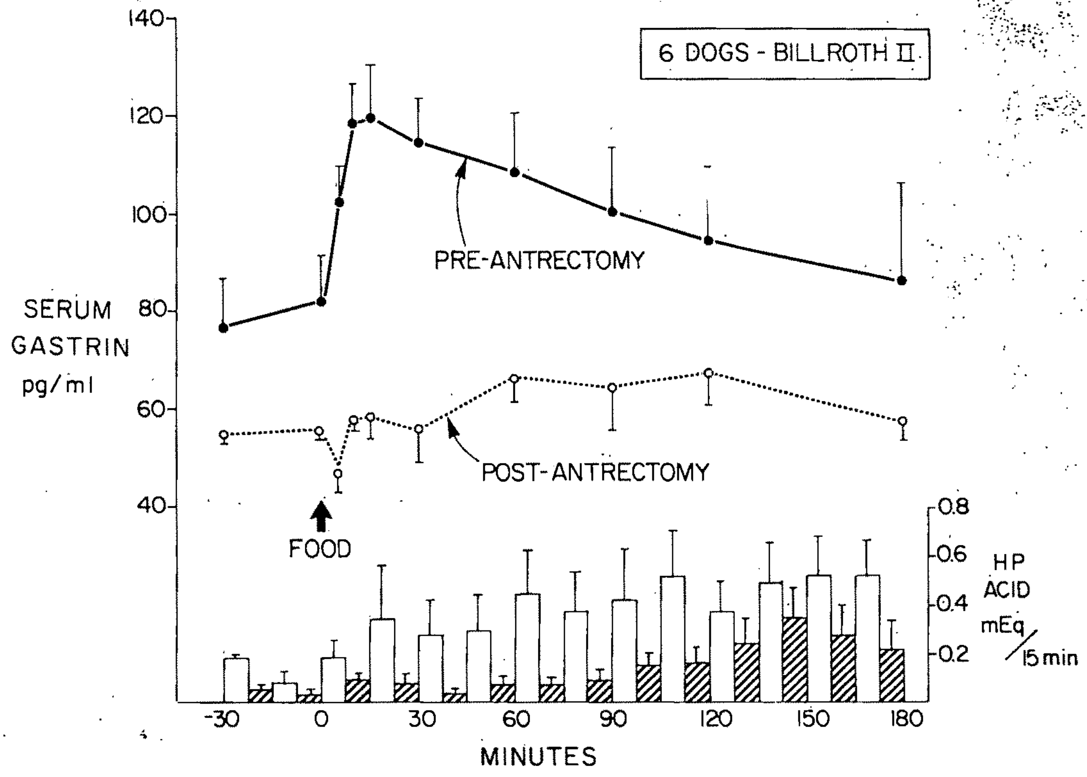

Fig. 2. Basal and postprandial serum gastrin and Heidenhain pouch acid values in six dogs before and after antrectomy with gastrojejunostomy (Billroth II). Pre-antrectomy acid values are shown by the open bars and postantrectomy values are shown by the striped bars.

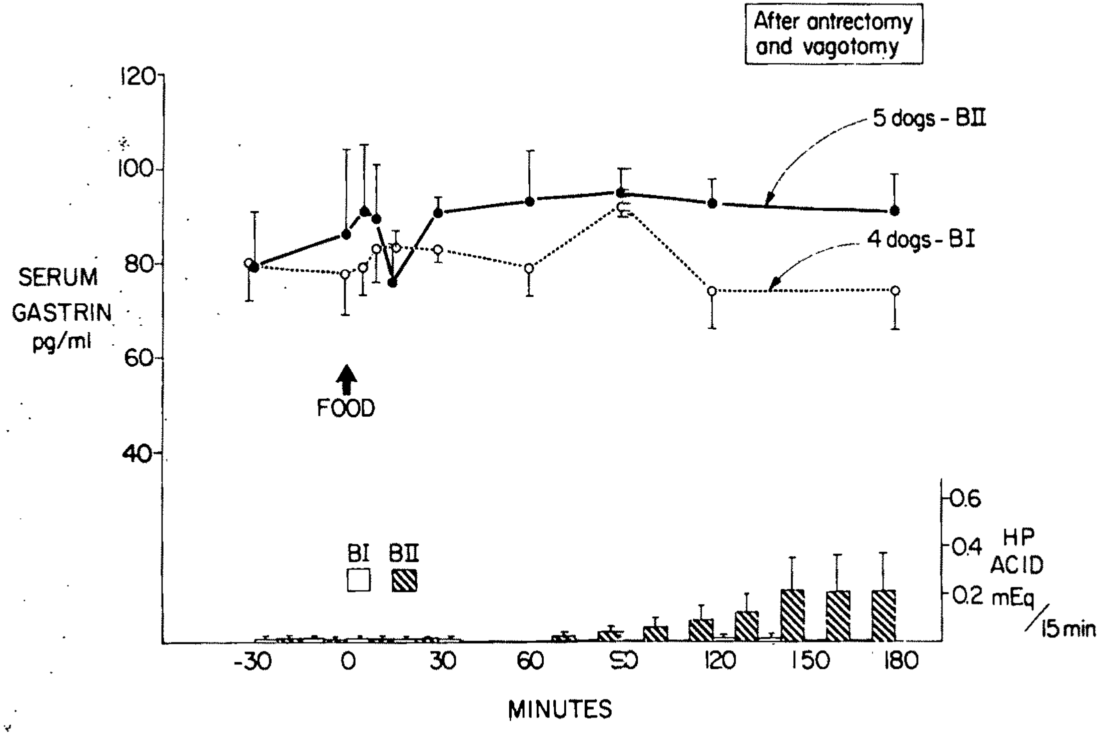

Fig. 3. Basal and post-prandial serum gastrin and Heidenhain pouch acid values after antrectomy *and vagotomy* in five dogs with antrectomy and gastrojejunostomy (B II) and four dogs after antrectomy and gastroduodenostomy (B I). Acid values in vagotomized dogs with antrectomy and Billroth I anastomosis are shown by the open bars and acid values in vagotomized dogs with antrectomy and Billroth II anastomosis are shown by the striped bars.

The half-life of gastrin, both exogenous[16] and kinetic endogenous,[11,23] is known to be short. Catabolic mechanisms which probably contribute to the short half-life have been identified in the fundus of the stomach,[7] the small bowel[2] and the kidney;[5] basal concentrations of gastrin are apparently not affected by transit of these organs[22] as reflected by the prolonged half-life of big big gastrin (9[illegible] min, Yalow[26]).

Extra-antral gastrin is known to exist within the gastric fundus,[25] small bowel[4,12,25] and pancreas.[8,12] In man, high concentrations of gastrin have been found in the proximal small bowel, especially within the proximal duodenum.[15] Gastrin can be released from the proximal duodenum and jejunum in dogs by locally applied agents,[3] but the mechanisms of release are not well understood. If they are under the same stimulatory and inhibitory controls that are known to influence the release of antral gastrin, it is difficult to understand why food, the most potent physiologic releasing agent for antral gastrin, failed to elicit increased levels of serum gastrin after antrectomy.

Abolition of the post-prandial rise in serum gastrin by antrectomy indicates that the proximal intestine does not make a major contribution to post-prandial increases in serum gastrin in dogs although it seems clearly to occur in man.[1,4,10,18] This suggests a most important species difference in response to feeding. Recent studies in dogs[24] have shown that the post-prandial rise in serum gastrin is lowered by truncal vagotomy. This contrasts strongly with the findings in man in whom a marked post-prandial rise in serum gastrin was recorded after vagotomy and pyloroplasty.[1] The role of the vagus in controlling the release of gastrin in man may be importantly related to these species differences. Studies in man have suggested that truncal vagotomy causes significant post-prandial gastrin release from extra-gastric sites.[10] The present studies show clearly that this is not true in dogs since vagotomy following antrectomy did not influence the postprandial levels of serum gastrin. In other studies in dogs with denervated antral pouches,[19] vagal stimulation by sham feeding or insulin-induced hypoglycemia did not appear to release detectable amounts of extra-antral gastrin.

Antrectomy greatly diminished the HP acid output after food in the Billroth I dogs and nearly abolished it in the Billroth II group. The difference presumably is due to duodenal inhibitory mechanisms (secretin and others) which are operative in dogs after gastroduodenostomy and are presumably lost in dogs with gastrojejunostomy. In man, it has been suggested[17] that the serum gastrin response to food is lost in antrectomized patients with a Billroth II anastomosis but that the response persists in Billroth I patients. Another study,[10] however, has reported significant increases in gastrin levels in post-antrectomy patients with a gastrojejunostomy. There was no difference in the present study in the serum gastrin levels (basal and post-prandial) in the Billroth I and Billroth II groups.

Vagotomy after antrectomy caused no change in the previous greatly reduced HP acid output after food. This finding is different from that of Middleton and coworkers[17] who found that vagotomy increased the HP acid output in gastrectomized dogs. The reason for the difference is unexplained.

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Determinants of Cardiac Output During Experimental Therapeutic Hemodilution

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(With the technical assistance of Clarence Moore, Herbert Lundberg,
Leon Turner, B.S., M.S., Herbert Williamson, and Calvin Scott, B.S.)

In 20 dogs, blood loss of 20 ml/kg during thoracotomy was immediately replaced with 40 ml/kg of 2.5% dextran-40 or dextran-70 in saline. An immediate rise in blood volume, associated with a decrease in hematocrit and blood viscosity, produced a marked rise in cardiac output. This effect was slightly greater with dextran-40. During the first four hours after infusion of dextran-40, both blood volume and cardiac output fell below control levels. Blood volume and cardiac output remained at or near control levels during this period in the group receiving dextran-70. In both groups, blood viscosity and hematocrit remained low throughout the study, but cardiac output increased only in response to an increase in blood volume. Twenty-four hours after infusion of either dextran-40 or dextran-70, hematocrit had decreased further, presumably due to postoperative blood loss while blood volume and cardiac output remained at or near control levels. During isovolemic hemodilution in this experimental setting, cardiac output responded primarily to changes in blood volume rather than blood viscosity. Therefore, decreased oxygen availability during hemodilution was compensated only by a rise in oxygen extraction.

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In UNTREATED HEMORRHAGE, normal cardiac output may be restored at a subnormal blood volume by "physiological" hemodilution.[3] During the first 24 hours after blood loss, plasma protein and extravascular fluid enter the circulation by transcapillary refilling, reducing the hematocrit as plasma volume rises. The resulting hemodilution causes reduced blood viscosity and decreased vascular resistance, thus increasing venous return. Cardiac output returns to normal, although blood volume may remain below control levels.[3]

Therapeutic hemodilution represents an attempt to achieve this compensatory state in the immediate post-hemorrhage period by replacing lost volume with plasma-expanding solutions. Drucker and associates[7] showed that therapeutic hemodilution was not associated with a significant oxygen debt, despite the reduction in circulating red cell mass. Numerous studies performed subsequently showed that cardiac output rose above control levels during acute hemodilution, presumably due to a decrease in systemic vascular resistance.[1,2,6,9] Increased cardiac output associated with decreased vascular resistance has also been noted in chronic anemia.[8] Studies performed in this laboratory have revealed that immediate restoration of blood volume by plasma expanders after hemorrhage caused a marked rise in cardiac output, decreased blood viscosity and decreased vascular resistance.[1] Cardiac output decreased below control levels, however, as blood volume decreased during the first two hours after infusion. The decrease in blood volume was related to the use of dextran-40 (2.0% in saline) or saline for volume expansion. These solutions rapidly leave the intravascular compartment after infusion.

In earlier studies[6] a 2.5% solution of dextran-40 in saline was found to adequately support the circulation for two hours after hemorrhage, when given a volume equal to twice the blood loss. The use of a 2.5% solution of dextran-40 in saline allows the infusion of adequate crystalloid to expand the extracellular space, and adequate colloid to maintain intravascular volume. This concentration also keeps the dose of dextran-40 below 1 gm/kg. Doses higher than 1 gm/kg have been associated with increased bleeding during surgical procedures.

The present studies were intended to expand our previous observations by comparing the effects of 2.5% dextran-40 and dextran-70 for 24 hours after their substitution for blood

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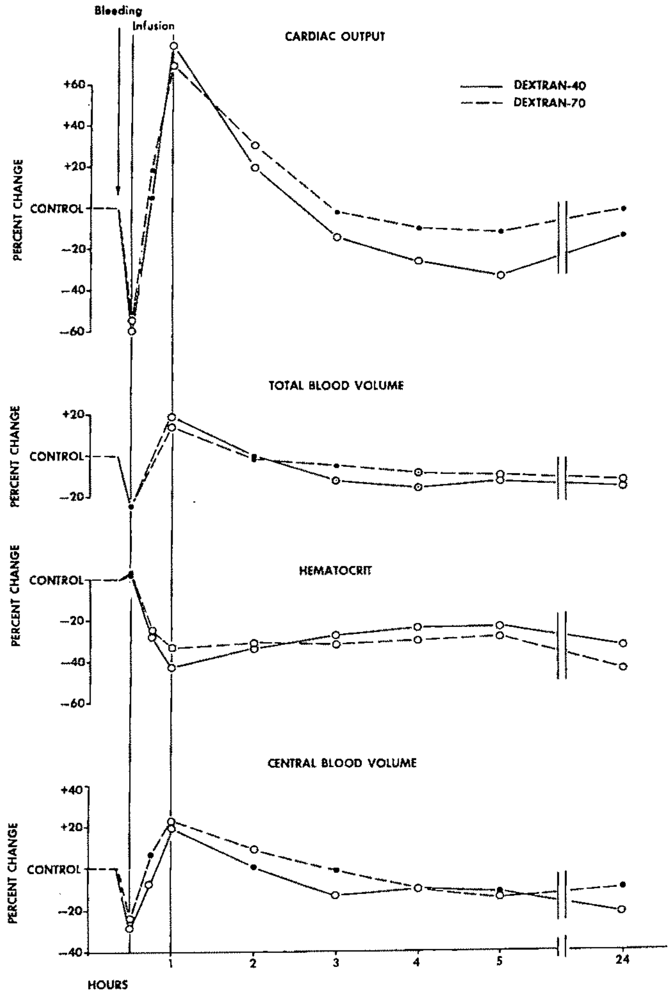

FIG. 1. Hemodynamic changes after substitution of acute blood loss (20 ml/kg) with 2.5% dextran-40 or dextran-70 (40 ml/kg). Open circles = $p < .05$. Each line represents the mean of ten experiments

loss. The larger average molecular weight of dextran-70 solutions would be expected to maintain blood volume more nearly at control levels, thus providing an opportunity to observe the hemodynamic effect of normovolemic hemodilution over a longer period of time. The studies were performed in anesthetized thoracotomized dogs in order to study the effect of therapeutic hemodilution in a simulated surgical setting.

Methods

Healthy mongrel dogs weighing 15–24 kg were anesthetized with sodium pentobarbital. Light anesthesia was maintained during the study periods. Polyethylene catheters were placed into the right atrium through the jugular vein and into the aorta through the femoral artery. Thoracotomy was performed in the right 5th intercostal space using sterile operative technique. Catheters were placed into the left atrium through a pulmonary vein and into the pulmonary artery through a branch of the right main pulmonary artery. Ventilation was controlled with an endotracheal tube and a Harvard respirator. After each sampling period, the lungs were gently re-expanded in order to avoid atelectasis.

After a 30 minute control period, the animals were rapidly bled 20 ml/kg of body weight. During the next 30 minutes, blood loss was replaced with 40 ml/kg of either 2.5% dextran-40 or 2.5% dextran-70 in saline. Ten experiments were performed with each solution. Cardiac output, intravascular pressures and arterial and mixed venous blood gases were measured three times during the control period, immediately after bleeding and at 15, 30, 90, 150, 210 and 270 minutes after bleeding. The chest was closed

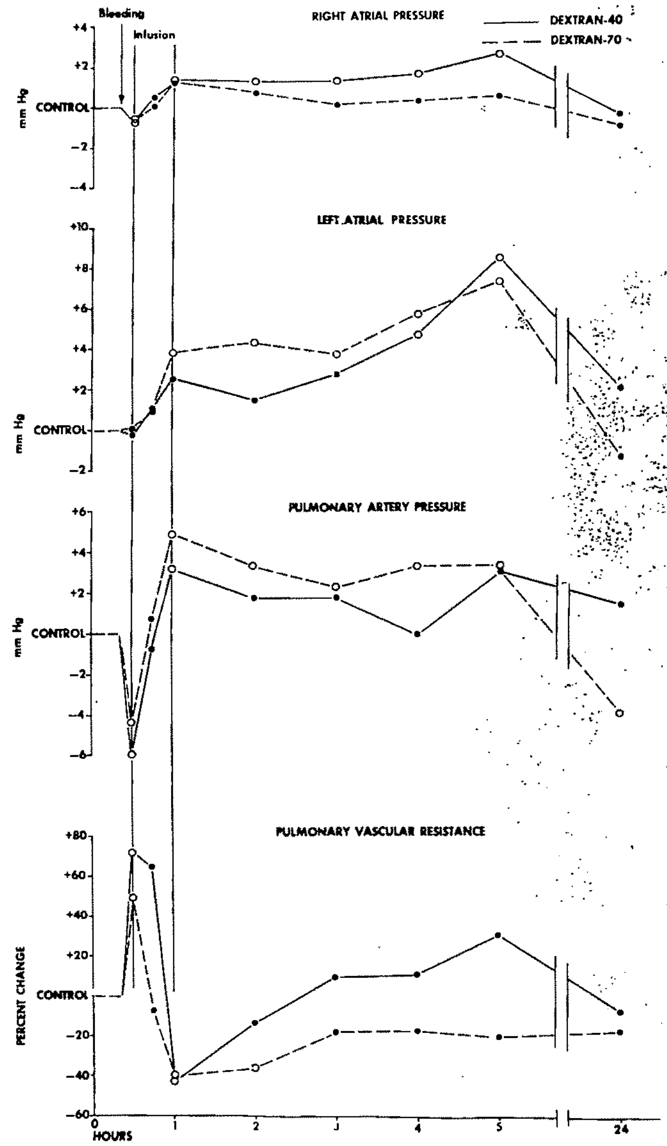

FIG. 2. Hemodynamic changes after substitution of acute blood loss (20 ml/kg) with 2.5% dextran-40 or dextran-70 (40 ml/kg). Open circles = $p < .05$. Each line represents the mean of ten experiments.

TABLE 1. *Hemodynamic and Metabolic Data*

Variable	Group	Control	Immediately after Bleeding	During Infusion (min.) 15	30
Cardiac Output (ml/kg/min)	D-40	130 ± 11	54 ± 7°°	137 ± 11	234 ± 17°°
	D-70	159 ± 16	72 ± 10°°	188 ± 28	270 ± 28°°
Total Blood Volume (ml)	D-40	2005 ± 104	—	—	2385 ± 120°°
	D-70	2065 ± 87			2355 ± 160°°
Hematocrit (%)	D-40	45 ± 1	47 ± 2	33 ± 2°°	26 ± 2°°
	D-70	44 ± 2	45 ± 2	33 ± 2°°	30 ± 2°°
Central Blood Volume (ml)	D-40	391 ± 29	279 ± 23°°	365 ± 17	467 ± 29°°
	D-70	436 ± 48	331 ± 45°°	465 ± 60	540 ± 64°°
Right Atrial Pressure (mm Hg)	D-40	10.4 ± 2	9.6 ± 2°	10.8 ± 2°	11.6 ± 2
	D-70	8.0 ± 2	7.3 ± 2°	8.1 ± 2	9.3 ± 1°
Left Atrial Pressure (mm Hg)	D-40	12 ± 2	12 ± 2	13 ± 3	15 ± 4
	D-70	10 ± 2	10 ± 3	10 ± 3	13 ± 3°°
Pulmonary Artery Pressure (mm Hg)	D-40	27 ± 3	21 ± 2°°	26 ± 3	30 ± 3°°
	D-70	24 ± 3	20 ± 3°	25 ± 3	29 ± 3°°
Pulmonary Vascular Resistance (mm/Hg/L/min)	D-40	5.5 ± 0.9	9.4 ± 2.4°	9.0 ± 4.7	3.2 ± 0.5°°
	D-70	4.4 ± 0.5	6.6 ± 0.9°	3.6 ± 0.4	2.6 ± 0.3°°
Systemic Arterial Pressure (mm Hg)	D-40	158 ± 5	117 ± 12°°	157 ± 5	163 ± 7
	D-70	161 ± 7	129 ± 14°	158 ± 6	168 ± 5°
Systemic Vascular Resistance (mm/Hg/L/min)	D-40	53 ± 5	91 ± 7°°	50 ± 5	30 ± 3°°
	D-70	47 ± 6	83 ± 10°°	41 ± 5°	30 ± 4°°
Stroke Volume Index (ml/kg)	D-40	0.8 ± 0.08	0.4 ± 0.04°°	0.9 ± 0.07	1.3 ± 0.10°°
	D-70	0.9 ± 0.08	0.4 ± 0.05°°	1.1 ± 0.13	1.4 ± 0.13°°
Heart Rate (beats/min)	D-40	171 ± 9	158 ± 13	159 ± 8°	176 ± 7
	D-70	186 ± 8	181 ± 11	174 ± 6°	188 ± 6
Total Cardiac Work (Kg-M/min.)°°	D-40	8.0 ± 0.8	2.7 ± 0.5°°	8.4 ± 0.9	16.9 ± 2.0°°
	D-70	9.8 ± 1.0	3.9 ± 0.9°°	11.4 ± 2.0	18.8 ± 2.2°°
Actual Viscosity°°° Centipoise 23 sec −1	D-40	6.8 ± 0.3	—	—	3.5 ± 0.3°°
	D-70	6.2 ± 0.4			4.1 ± 0.4°°
Corrected Viscosity°°° Centipoise 23 sec. −1	D-40	6.8 ± 0.3	—	—	6.9 ± 0.3
	D-70	6.2 ± 0.4			7.1 ± 0.3°
Base Excess (meq/L)	D-40	−7.6 ± 1.1	−9.1 ± 1.0°°	−9.5 ± 1.0°	−9.7 ± 0.8°°
	D-70	−6.4 ± 1.3	−7.7 ± 0.9°	−9.1 ± 1.0°°	−9.3 ± 1.0°°
Oxygen Consumption (ml/kg/min)	D-40	5.6 ± 0.6	4.1 ± 0.6°	5.6 ± 0.6	6.5 ± 0.9
	D-70	6.0 ± 0.9	4.7 ± 2.6°	7.0 ± 1.6	8.3 ± 1.0°°

All values expressed as mean ± standard error for each group.
D-40 = Dextran − 40; D-70 = Dextran − 70.
°p < .05.
°°p < .01.
°°°Actual Viscosity = viscosity of unmodified whole blood.
°°°Corrected Viscosity = viscosity of whole blood after restoration to control hematocrit value.

two hours after bleeding and the animals were allowed to recover 4½ hours after bleeding. Blood volume and blood viscosity were determined during the control period and at hourly intervals during the first four hours after hemorrhage. Blood removed for sampling was carefully replaced using blood removed at the time of hemorrhage.

Twenty-four hours after being bled the animals were again anesthetized and placed on controlled ventilation and all measurements were repeated.

Pressures were monitored electronically with transducers and a photographic recorder. Cardiac output was determined by dye-dilution technique using indocyanine green as the indicator. Arterial blood withdrawn during measurement of cardiac output was reinfused. Samples for blood gas determination were withdrawn from the aorta and the pulmonary artery. Arterial and venous pH, PO_2, and PCO_2 were determined on an Instrumentation Laboratory blood gas analyzer. Base excess was determined from the Siggaard-Andersen nomogram. Oxygen content was determined from the PO_2, oxygen saturation, and the hemoglobin concentration (as estimated from the hematocrit). Oxygen consumption was determined by multiplying the arteriovenous oxygen difference by the cardiac output. Blood volume was determined from the dilution of radioactive iodinated serum albumin (5uc) with a semi-automated blood volume computer. Whole blood viscosity was determined on a Brookfield cone-plate viscometer. Cardiac output curves were manually digitized and cardiac output and mean transit time were calculated off-line by computer from standard formulas. Central blood volume and other hemodynamic variables were calculated by including appropriate options (heart rate and intravascular pressures) in the computer program. Total cardiac work (TCW) was calculated by determining pressure and kinetic wock for each ventricle as previously descirbed. The technique and accuracy of these methods have been described in previous publications.[8,9]

Statistical analysis was performed by calculation of the

Hours Postinfusion				
1	2	3	4	24
156 ± 13°°	113 ± 11°	97 ± 10°°	89 ± 10°°	115 ± 13
208 ± 22°°	157 ± 15	144 ± 17	140 ± 17	160 ± 15
2005 ± 147	1765 ± 89°°	1705 ± 86°°	1770 ± 97°°	1730 ± 109°°
2035 ± 107	1975 ± 136	1900 ± 109	1890 ± 117°	1800 ± 117°°
30 ± 2°°	33 ± 2°°	34 ± 2°°	35 ± 2°°	31 ± 2°°
30 ± 1°°	31 ± 1°°	31 ± 2°°	33 ± 1°°	26 ± 1°°
392 ± 32	340 ± 27°	358 ± 49	349 ± 53	311 ± 32°°
476 ± 57°	434 ± 65	398 ± 55°°	376 ± 47°°	400 ± 34
11.7 ± 2°	11.7 ± 2°	12.0 ± 2°	12.9 ± 2°	10.0 ± 2
8.7 ± 2	8.2 ± 2	8.4 ± 2	8.6 ± 2	7.4 ± 2
14 ± 3	15 ± 4	17 ± 3°°	17 ± 4°	11 ± 5
14 ± 3°	13 ± 3°	15 ± 4°°	17 ± 3°°	6 ± 2
29 ± 3	29 ± 3	27 ± 3	26 ± 2	23 ± 5
28 ± 3°°	26 ± 3°	27 ± 3°	27 ± 3°	17 ± 1°
4.7 ± 0.9	6.0 ± 1.1	6.1 ± 1.8	5.1 ± 2.0	4.5 ± 0.8
2.9 ± 0.4°	3.7 ± 0.5	3.7 ± 0.4	3.5 ± 0.5	3.3 ± 0.7
169 ± 6°	164 ± 6	165 ± 7	160 ± 8	140 ± 8°
178 ± 7°°	173 ± 8°	173 ± 7°	173 ± 5°	137 ± 5°°
47 ± 4°	65 ± 8°	80 ± 13°	81 ± 10°°	51 ± 5
40 ± 4°°	51 ± 6	57 ± 7°	58 ± 6°	39 ± 4
0.9 ± 0.08°	0.6 ± 0.06°°	0.5 ± 0.06°°	0.5 ± 0.06°°	0.7 ± 0.08
1.1 ± 0.10°°	0.9 ± 0.10	0.9 ± 0.13	0.7 ± 0.08	1.1 ± 0.11°
185 ± 7°	183 ± 8	188 ± 9°	188 ± 9°	180 ± 7
197 ± 6°	186 ± 8	187 ± 8	190 ± 7	152 ± 7°°
10.5 ± 1.2°°	7.3 ± 1.0	6.1 ± 0.9°°	5.3 ± 0.9°°	5.8 ± 0.9°
14.9 ± 2.1°°	10.7 ± 1.4	9.6 ± 1.3	8.9 ± 0.9	8.4 ± 0.9
4.2 ± 0.3°°	4.6 ± 0.2°°	4.5 ± 0.2°°	4.6 ± 0.3°°	4.4 ± 0.4°°
4.4 ± 0.3°°	4.5 ± 0.3°°	4.8 ± 0.3°°	5.0 ± 0.4°°	3.5 ± 0.2°°
6.6 ± 0.3°°	6.6 ± 0.3	6.4 ± 0.3	5.9 ± 0.6	6.5 ± 0.8
7.2 ± 0.4°°	7.2 ± 0.5°	7.0 ± 0.3°	7.6 ± 0.5°	6.7 ± 0.4
−9.4 ± 0.9°°	−9.0 ± 1.1°	−9.0 ± 1.2	−8.2 ± 0.7	−5.5 ± 0.6
−8.4 ± 0.9°	−8.0 ± 0.9°	−8.4 ± 0.7	−8.0 ± 1.0°	−7.6 ± 0.9
5.2 ± 0.5	4.6 ± 0.5	4.5 ± 0.4°	4.0 ± 0.5°	4.3 ± 0.5
7.3 ± 1.2°	5.6 ± 1.0	6.5 ± 1.2	6.7 ± 1.6	6.2 ± 1.3

mean, standard deviation, and standard error for the combined results obtained in each group of dogs. The significance of the results was determined by calculating the t value for the mean change observed at each sampling period as it compared to the mean of the three control samples.

Results

The results are summarized in Table 1 and Figs. 1-6. Cardiac output increased markedly during infusion, as total blood volume and central blood volume rose and hematocrit decreased (Fig. 1). The intital response was slightly greater in animals receiving dextran-40. During the next four hours, hematocrit remained approximately 25% below control levels. Total blood volume and central blood volume returned to control levels within two hours after infusion of the dextran-70. In animals receiving dextran-40, however, both total volume and central blood volume were slightly decreased ($p < .05$) at this point. Two hours after infusion, cardiac output returned to control levels in the dextran-70 group, but in the dextran-40 group cardiac output was decreased ($p < .05$). Twenty-four hours after infusion, cardiac output returned to control levels in both groups while hematocrit and total blood volume were decreased.

Right atrial, left atrial and pulmonary artery pressures increased after infusion in both groups, remained elevated for the first four hours and returned to control levels 24 hours after infusion (Fig. 2). Pulmonary vascular resistance was 40% below control levels immediately after infusion in both groups, but no statistically significant changes were recorded thereafter.

Systemic arterial pressures were slightly elevated after infusion of dextran-70 ($p < .05$), but unchanged after infusion of dextran-40 (Fig. 3). Systemic vascular resistance was initially decreased after infusion by approximately 40% in both groups, then rose above control levels two to four hours later. Twenty-four hours after infusion, systemic arterial pressure and resistance were slightly decreased in both groups.

Changes in stroke volume and total cardiac work were similar to changes in cardiac output, while heart rate remained at or near control levels throughout the study (Fig. 4).

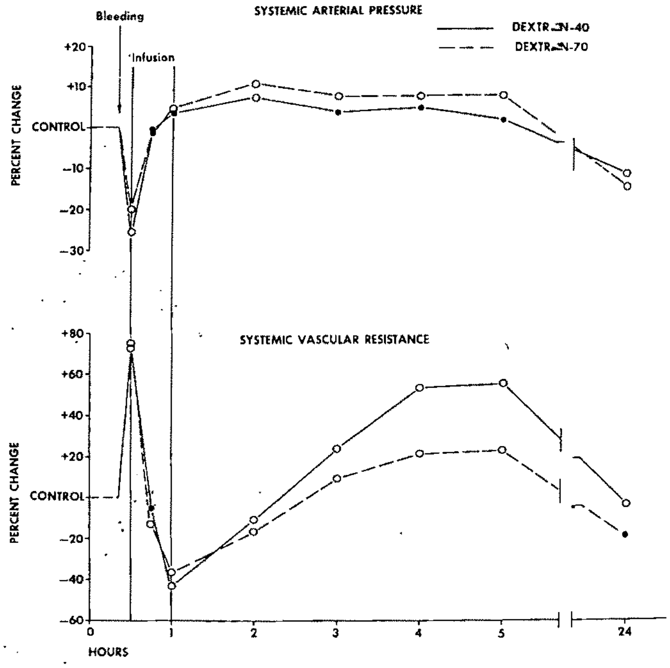

FIG. 3. Hemodynamic changes after substitution of acute blood loss (20 ml/kg) with 2.5% dextran-40 or dextran-70 (40 ml/kg). Open circles = $p < .05$. Each line represents the mean of ten experiments.

Whole blood viscosity decreased by 32% after infusion of dextran-70 and 48% after infusion of dextran-40 (Fig. 5). Whole blood viscosity rose slightly during the first four hours after infusion, but remained significantly decreased in both groups.[3] Viscosity at corrected hematocrit (hematocrit restored to control level) increased significantly after infusion of dextran-70, but remained at control levels in the dextran-40 group.

Base excess decreased slightly ($p < .05$) after infusion in both groups (Fig. 6). Base excess remained slightly decreased in the dextran-70 group, but rose 24 hours after infusion of dextran-40. Oxygen consumption increased transiently after infusion of dextran-70 ($p < .05$) but remained at or near control levels thereafter in both groups.

The relationship of cardiac output to hematocrit and blood volume was tested by regression analysis. All measurements of cardiac output during isovolemic hemodilution (blood volume ± 10% of control) were plotted against hematocrit (Fig. 7.). In spite of marked decreases in hematocrit, little change in cardiac output was observed. In particular, the graphs show few measurements significantly above the zero point for cardiac index. Changes in blood volume, however, correllated well with changes in cardiac output (Fig. 8), particularly in animals receiving dextran-40.

Discussion

Acute hemodynamic studies have indicated that increased cardiac output compensates for the reduction in arterial oxygen content caused by hemodilution.[1,2,6,9] In addition, Messmer and associates[10] have reported that tissue metabolism of oxygen has not been impaired. Thus, it has been assumed that replacement of blood loss with plasma expanders caused no reduction in oxygen availability to the tissues. Experimental and clinical data from our laboratory, however, have indicated that blood volume deficits may occur several hours after replacement of blood loss with plasma volume expanders.[2]

The present studies represent at attempt to find a satisfactory method of inducing hemodilution in a simulated surgical setting. In previous studies, dextran-40 was only temporarily effective because of its transient volume expanding effect. Increased blood loss was also associated with its use in our clinical studies.[2] This problem was unexpected, because the dose of dextran was limited to less than 1 gm/kg, a dose not associated with measurable changes in coagulation studies. However, it is likely that the physical effects of hemodilution (decreased blood viscosity, increased capillary flow) and the anti-platelet-adhesiveness effect of dextran-40 combine to cause increased blood loss in the presence of open wounds. In the present studies, both

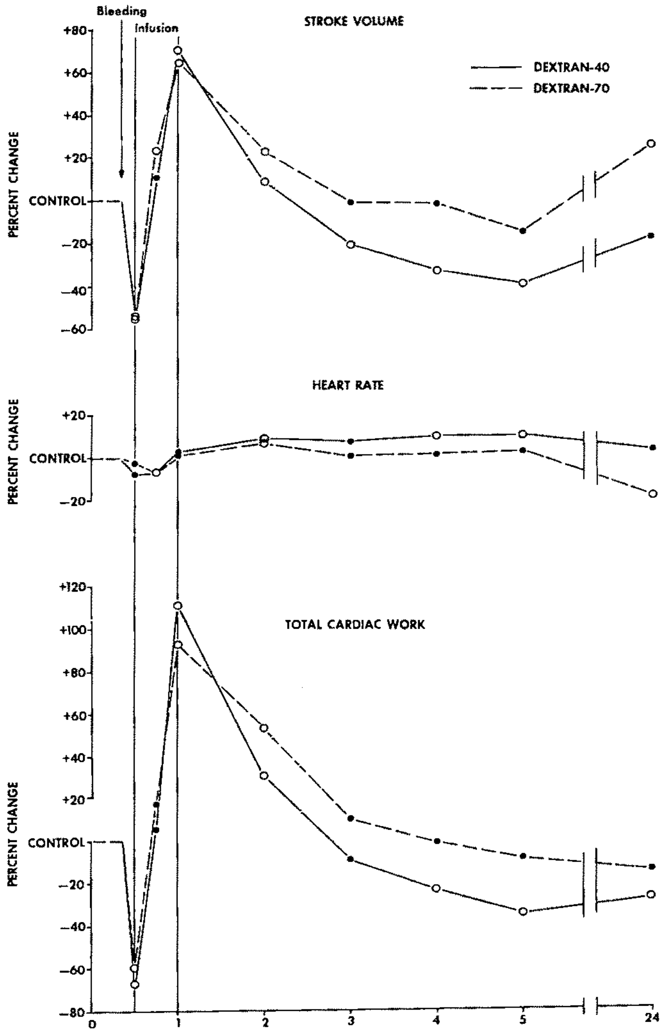

FIG. 4. Hemodynamic changes after substitution of acute blood loss (20 ml/kg) with 2.5% dextran-40 or dextran-70 (40 ml/kg). Open circles = $p < .05$. Each line represents the mean of ten experiments.

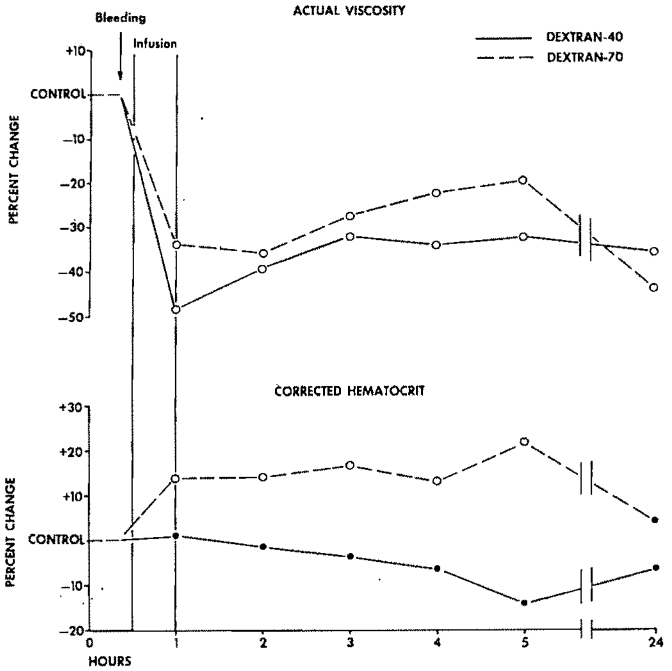

FIG. 5. Changes in whole blood viscosity ("actual viscosity") and viscosity of blood restored to control hematocrit ("corrected hematocrit"). Open circles = $p < .05$. Each line represents the mean of ten experiments.

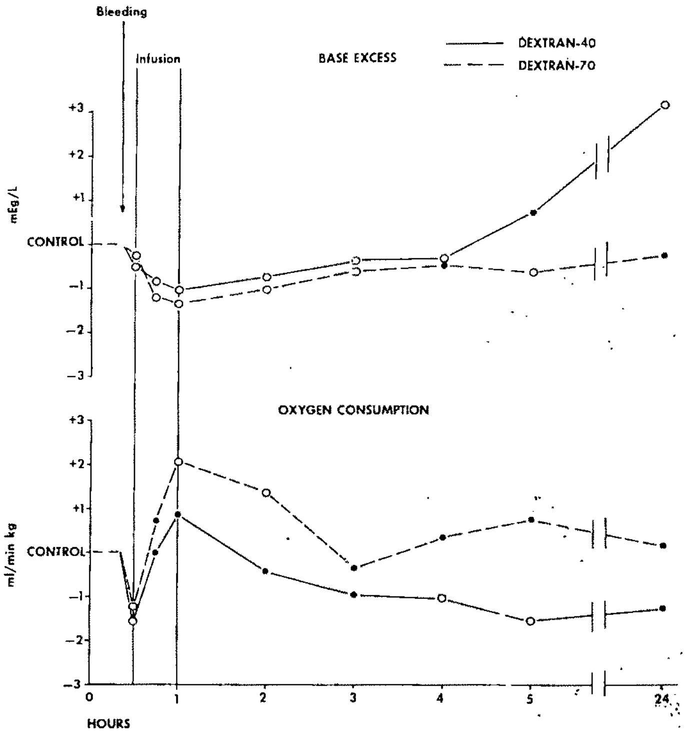

FIG. 6. Metabolic changes during therapeutic hemodilution. Open circles = $p < .05$. Each line represents the mean of ten experiments.

dextran-40 and dextran-70 were associated with moderate blood loss during the first 24 hours after infusion: hematocrit dropped from 35 to 31 in the dextran-40 group, and from 33 to 26 in the dextran-70 group, during the first 24 hours without change in total blood volume. In spite of the fact that hemodynamics were somewhat better in the dextran-70 group, there was little noticeable difference between the groups in their ability to tolerate the procedure.

The immediate hemodynamic effect of blood substitution by dextran is a marked rise in cardiac output, associated with reduced blood viscosity and vascular resistances. Blood is shifted to the central circulation, as indicated by a rise in central blood volume and increased atrial and pulmonary artery pressures. The cardiac output rise is a Starling response as indicated by a rise in stroke volume and cardiac work with no change in heart rate or systemic arterial pressure. Although both dextran-40 and dextran-70 reduced blood viscosity by hemodilution, viscosity of whole blood at corrected hematocrit was significantly above control after infusion of dextran-70. This observation might be of

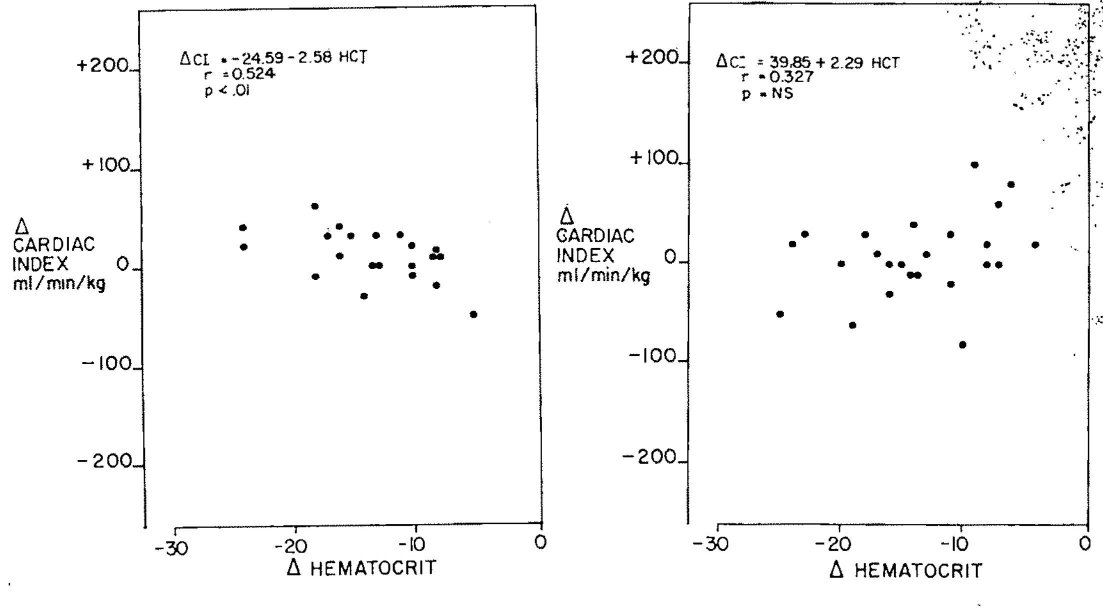

FIG. 7. Correlation of the changes in cardiac index with the change in hematocrit during isovolemic hemodilution. (Blood volume ± 10% of control) (Left) Dextran-40. (Right) Dextran-70.

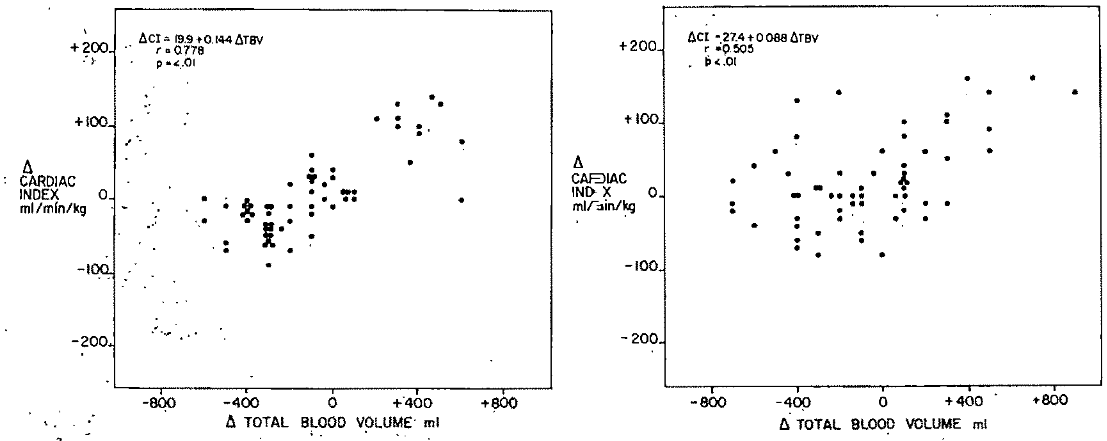

FIG. 8. Correlation of the change in cardiac index with the change in blood volume during therapeutic hemodilution. (Left) Dextran-40. (Right) Dextran-70.

significance only if dextran-70 were infused over several days at a normal hematocrit, thus allowing higher molecular weight fractions of dextran to accumulate.

Total oxygen consumption was adequately maintained by this method of hemodilution. However, after the initial overshoot, cardiac output returned rapidly to control levels in spite of the maintenance of hemodilution and (in the case of dextran-70) normovolemia. A rise in systemic vascular resistance occurred during the first four hours after infusion, although blood viscosity remained decreased. This observation suggests that vasoconstriction occurs to compensate for the decrease in blood viscosity. Pavek and associate [11] have reported redistribution of regional blood flow after acute hemodilution, implying that regional vascular resistances undergo marked changes as well. In Pavek's studies, the less active vascular beds, such as heart and muscle, retained increased flow during the later stages of acute hemodilution, while flow was reduced to the splanchnic and renal circulations. If total systemic blood flow is normal during "chronic" hemodilution, some regional beds must have reduced flow to compensate for the redistribution to muscle beds. Presumably, this may occur in "chronic" hemodilution as well.

Two to four hours after hemodilution with dextran-70 and 24 hours after hemodilution in both groups normovolemia was accompanied by normal cardiac output. Since arterial oxygen content is decreased by hemodilution, these studies also indicate that systemic oxygen availability (arterial oxygen content X cardiac output) is reduced. Pavek and Carey[12] showed that isovolemic hemodilution was always accompanied by reduced oxygen availability because total systemic flow remained near normal. The present studies substantiate this finding. In spite of hemodilution, cardiac output varied primarily with blood volume rather than hematocrit.

These observations may have clinical implications for the use of isovolemic hemodilution in patients with reduced cardiac output, arterial oxygen content, or both (reduced oxygen availability), prior to operation. In the absence of increased cardiac output, oxygen consumption is maintained only by increased oxygen extraction. Patients with reduced oxygen availability might develop a systemic or regional oxygen debt (particularly in areas of reduced flow) if oxygen extraction does not adequately increase during blood substitution with plasma expanders.

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Efficacy of Intravenous Clindamycin and Methicillin in Gram-positive Soft Tissue Infections

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In a comparative study on a general surgical service, intravenous clindamycin phosphate or methicillin was used to treat a variety of soft tissue infections due to gram-positive organisms, chiefly staphylococci. The infections were rated according to severity, responsible organisms, and site of the infection. Excellent or good clinical and bacteriologic responses were obtained with both clindamycin and methicillin as adjuncts to basic surgical therapy in these soft tissue infections. The adverse effects of each drug were detailed, and were comparable. Clindamycin phosphate is a satisfactory substitute for methicillin in soft tissue infections secondary to gram-positive organisms.

SOFT TISSUE INFECTIONS of the extremities are common and significant causes of morbidity. The infecting organisms are commonly staphylococci and streptococci which gain access to the subcutaneous tissues following trauma. Most staphylococci, including coagulase-negative strains, are resistant to penicillin G, and alternate therapy with a penicillinase-resistant penicillin or another drug is indicated.

Clindamycin,[*] an analog of lincomycin, displays greater activity than lincomycin against *Staphylococcus aureus* and other gram-positive pathogens *in vitro*.[10,11,18] It acts by interfering with protein synthesis intracellularly and can be bacteriostatic or bactericidal *in vitro*, depending upon the concentration of the antibiotic and the sensitivity of the organism.[22] The drug is widely distributed in fluids and tissues, including bone, after administration of an oral dosage form.[17] Higher serum levels of clindamycin can be achieved with parenteral dosing with clindamycin phosphate; this preparation is rapidly hydrolyzed to clindamycin *in vivo*.[7]

Methicillin, which was the first of the penicillinase-resistant penicillins, has become well established as an antistaphylococcal drug in the past decade. From their pharmacologic properties and *in vitro* activity against the usual gram-positive pathogens, it could be predicted that methicillin and clindamycin would show similar efficacy in soft tissue infections due to such organisms. The purpose of this study was to compare results of treatment with intravenously administered clindamycin phosphate and sodium methicillin[†] in soft tissue infections in patients on a general surgical service.

Materials and Methods

One-hundred and ten hospitalized patients gave their informed consent in writing to enter the comparative study. Reasons for exclusion from the study were allergy to penicillin or penicillin derivatives or allergy to clindamycin or lincomycin. Patients were assigned to treatment with clindamycin or methicillin by use of a table of random numbers. The dosage of clindamycin phosphate ranged 600–1000 mg[‡] every 6 hours; methicillin dosage ranged 500–1000 mg every 6 hours. Both drugs were administered intravenously.

Sixty-nine patients completed their course of therapy, but only 53 met all of the criteria for efficacy evaluations, including the following: admission cultures demonstrated a gram-positive organism; soft tissue sites, usually ex-

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[*] Cleocin® is The Upjohn Company's U.S. registered trademark for clindamycin, which is 7(s)-chloro-7-deoxylincomycin; outside of the U. S. A. clindamycin is also marketed as DALACIN C® (Canada) or SOBELIN®.

[†] Staphcillin® (Bristol).

[‡] Dosages and serum concentrations in this paper are stated in terms of clindamycin base equivalents.

TABLE 1. *Severity of Infections in all Patients and in Those Who Met All Study Criteria*

Severity of Infection	Clindamycin All Patients	Clindamycin Completed Study	Methicillin All Patients	Methicillin Completed Study
Mild	16	12 (37%)	11	8 (38%)
Moderate	24	19 (59%)	15	13 (62%)
Severe	1	0	0	0
Not rated	2	1	0	0
Total	43	32	26	21

tremities, were the focus of infection; and intravenous antibiotic therapy was maintained for four days or more. Antibiotic therapy was discontinued when the infection was cured. At the termination of therapy, repeat cultures were obtained whenever possible to document bacteriologic response. Data from 16 patients could not be evaluated because their initial cultures failed to show gram-positive organisms or they could not complete four days of intravenous therapy.

Clinical laboratory determinations performed at the beginning of antibiotic therapy and again at the end of parenteral therapy included the following: complete blood count; urinalysis; and measurement of serum urea nitrogen, serum creatinine, serum alkaline phosphatase, and serum glutamic oxalacetic transaminase (SGOT).

The numbers of patients assigned to each treatment and their distribution with respect to severity of infection are shown in Table 1. The average age of the clindamycin group was 48 years, and the average age of the methicillin group was 41. Of the patients completing the study, 25 in the clindamycin group were male and 7 were female, and 13 in the methicillin group were male and 8 were female.

Table 2 lists the organisms clutured from wound , and Table 3 lists the type of infection. Clinical response was judged on the basis of decrease in pain and swelling, reduction of fever, and healing of wounds. Bacteriologic response was determined by the persistance of organisms on repeat culture at the end of therapy. Antibiotic susceptibility was determined by disc sensitivity tests using 2-mcg clindamycin, 2-mcg erythromycin, 5-mcg methicillin and 2-mcg penicillin discs.[8]

Results

As shown in Table 4, the clinical response in cases which could be fully evaluated was judged to be excellent or good in 30 of 32 patients treated with clindamycin and all of 21 patients treated with methicillin. Eleven patients had persistent positive cultures at the end of therapy with intravenous clindamycin, and six at the end of methicillin therapy. The two clindamycin-treated patients whose clinical response was reported as poor did not show persistant organisms on followup culture at the end of therapy. One of these patients was a 34-year-old man who developed fever and cellulitis secondary to frostbite after 24 hours of exposure to cold; coagulase-negative staphylococci were isolated from blister material from the left foot. Fever and elevated white blood count persisted after 5 days of intravenous clindamycin phosphate therapy. The infection subsequently responded to treatment with Sulfamylon cream. The other patient was an 80-year-old woman with a past history of unexplained fevers. The bone of the 3rd phalanx of the toe was exposed when she was admitted to the hospital from a nursing home, and the wound yielded coagulase-negative staphylococci. After 4 days of clindamycin therapy, the lesion was dry, yielding no growth on culture, but fever persisted and the white blood cell count increased from 6,200 to 7,700 per cu mm.

Ninety-six per cent of the infecting organisms isolated were staphylococci and 4% were streptococci. Examination of the disc susceptibility of the staphylococci cultured (Table 5) prior to treatment shows that only 4 of the 50 staphylococcal isolates were resistant to clindamycin; 13 were resistant to erythromycin. Of the 13 strains which tested resistant to methicillin, only 3 were also resistant to clindamycin; the other clindamycin-resistant strain was susceptible to methicillin.

Thrombophlebitis developed in 6 (14%) of the 43 patients given clindamycin and 8 (24%) of the 32 given methicillin. This was not severe with either drug. Indwelling catheters (Intracath) may have contributed to local irritation in some cases in both groups.

Dizziness, dyspnea, and urticaria developed after each of two successive doses of clindamycin phosphate in a patient who received a total of nine 750 mg infusions. The second episode was also marked by wheezing. Clindamycin was discontinued. Three other systemic reactions in the clindamycin group, considered probably not related to the drug, were as follows: The patient with frostbite and secondary cellulitis developed bone marrow depression several days after antibiotic therapy; a 91-year-old woman developed microscopic hematuria; and an 80-year-old woman showed a drop in hematocrit. SGOT increased during clindamycin therapy from 62 to 130 units in a diabetic patient with gangrene and cellulitis of the left great toe, and from 42 to 190 units in a burn patient who underwent skin grafting during therapy. Two other clindamycin-treated

TABLE 2. *Organisms Cultured From the Wounds of Patients Before Treatment in Evaluatable Cases*

Organism	Clindamycin	Methicillin
Staphylococcus, coagulase-positive	17	8
Staphylococcus, coagulase unknown	0	1
Staphylococcus, coagulase-negative	14	12
Streptococcus (not speciated)	1	0
α-Hemolytic streptococcus	0	1
Total	32	22°

° Coagulase-positive and coagulase-negative staphylococci isolated in 1 case.

TABLE 3. *Type of Infection in Evaluatable Cases*

Disease	Clindamycin	Methicillin
Cellulitis	17	9
Infected wounds	12	10
Neck	0	1
Hand or arm	0	4
Foot or leg	4	1
Frostbite (foot)	1	0
Abscess	2	3
Amputation site	1	0
Infected ulcer	1	1
Infected gangrene	1	0
Animal bite	1	0
Human bite	1	0
Burns	3	2

patients had increases in SGOT within the normal (45 units or less) range. A 73-year-old woman developed a skin rash during methicillin therapy and the drug was discontinued after 8 doses. A 34-year-old man with stab wounds of the neck showed an increase in SGOT from 54 to 95 units during methicillin therapy.

Discussion

Clindamycin appears to be a potent antibiotic against organisms commonly encountered on a general surgical service. Its spectrum of activity *in vitro* includes most staphylococci, pneumococci and streptococci (except *Streptococcus faecalis*) and gram-positive and gram-negative anaerobes.[2,10,11,18] It has little or no activity against gram-negative aerobes.[16] Methicillin is active against most pneumococci, streptococci and staphylococci, except for some strains of staphylococci which are resistant not only to methicillin but to other penicillinase-resistant penicillins and numerous other antibiotics. Most of the methicillin-resistant strains that are multiply resistant are sensitive to lincomycin and clindamycin in vitro.[1,4,12,19] In our study 96% of the infecting organisms isolated were staphylococci. Of the 13 strains resistant to methicillin on disc testing, only 3 also tested resistant to clindamycin. Other laboratory studies would be required to characterize these strains which tested resistant to methicillin and to determine their precise antibiotic susceptibility pattern.

Studies by Carlisle and Saslaw[5,6] showed comparable results with parenteral clindamycin and methicillin in experimental staphyloccal and streptococcal infections in monkeys. In clinical trials, intramuscular or intravenous clindamycin phosphate was used in 131 patients in a study reported by Schumer and coworkers.[20] The initial pathogens were eradicated in 22 of 28 cases of postoperative wound infections and 11 of 14 cases of cellulitis, although not in 4 cases of infected gangrene. Compromised circulation was a factor in several of the soft tissue infections that failed to respond. Fass and Saslaw[9] also reported generally good results with parenteral clindamycin phosphate in soft tissue infections. Kerstein[14] described good results in soft tissue infections in 8 patients given intravenous clindamycin phosphate at Boston City Hospital; these were among the first patients to be treated intravenously with this drug.

A wide variety of soft tissue infections were treated in the comparative study on our general surgical service (Table 3). Despite the use of random numbers to assign patients to treatment, clindamycin was used more often in conditions less likely to benefit from antibiotic therapy, such as infected gangrene, amputations and frostbite. Nevertheless, the clinical and bacteriologic responses in the clindamycin and methicillin groups did not differ significantly, and clinical results were good in almost all cases. Although positive cultures could still be obtained at the end of parenteral therapy in some cases (Table 4), the lesions were healing and signs of infection were abating in these cases.

The dosages of clindamycin phosphate and methicillin used in this study were probably higher than necessary to achieve satisfactory tissue levels, judging from the serum levels attainable with lower doses.[7,9,12] In testing 5 staphylococcal strains in vitro, Wagnerova and Vacek[22] found that 6-8 hours of exposure to clindamycin at the minimum bactericidal concentration (MBC) was needed to sterilize the culture completely. The MBC was 0.78 mcg/ml or less in 120 of 125 strains of staphylococci, the highest value being 3.12 mcg/ml in one strain. Serum clindamycin concentrations exceeding these levels can be maintained readily with parenteral dosages of 300 mg clindamycin phosphate 3 or 4 times daily.[7,9] However, as emphasized by Carlisle and Saslaw,[5,6] in antibiotic therapy correlations are not perfect between *in vivo* results and in vitro susceptibilities and serum antibacterial activities. According to the manufacturers, the usual adult dose of Staphcillin is 1,000 mg every 6 hours, while recommended dosages of clindamycin phosphate range from 300 mg every 12 hours to 1,200 mg every 6 hours, depending upon the severity of infection and sensitivity of the infecting organism.

The patients receiving clindamycin phosphate experienced fewer local reactions (thrombophlebitis) than those receiving methicillin in our study. One methicillin-treated

TABLE 4. *Clinical Response, Bacteriologic Response, and Duration of Fever in Clindamycin and Methicillin Treated Patients*

	Clindamycin (32 Patients)		Methicillin (21 Patients)	
Clinical Response				
Excellent	18	(94%)	6	(100%)
Good	12		15	
Poor	2		0	
Bacteriologic Response				
Oganism eradicated	21	(65%)	15	(71%)
Organism not eradicated	11		6	
Duration of Fever (Days)				
Mean	1.09		1.5	
Range	0–5		0–4	

TABLE 5. *Antibiotic Sensitivities of Organisms Cultured*

Organism	No. Sensitive/No. Tested Clindamycin	Methicillin	Erythromycin	Penicillin
Staphylococcus, coagulase-positive	22/24	20/25	20/26	8/23
Staphylococcus, coagulase-negative	22/24	16/23	14/22	2/24
Staphylococcus epidermidis	2/2	1/2	0/2	0/2
α-Hemolytic strepotococcus	1/1	1/1	1/1	1/1
Streptococcus (variant sp)	0/1	0/1	0/1	0/1

patient developed a rash. In one clindamycin-treated patient the drug had to be discontinued because of systemic reactions marked by dizziness, dyspnea and urticaria. The bone marrow depression, hematuria and drop in hematocrit noted in one patient each in the clindamycin group were probably not related to clindamycin therapy. Elevations in SGOT may have been drug-related; such elevations have been reported previously during oral or parenteral clindamycin therapy in patients with infection.[9,13,21] However, DeHaan *et al.*[8] compared the incidence of SGOT elevations in 210 normal volunteers, half of whom received oral clindamycin and half, placebo. There was no statistically significant difference between drug- and placebo-treated subjects in the frequency of SGOT elevation.

Acknowledgment

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Stricture of the Anorectum in Crohn's Disease Involving the Colon

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Crohn's disease involving the colon was complicated by anorectal stricture in 12 of 160 patients (7.5%). The clinical features of these 12 patients have been evaluated and compared with 148 control patients. The average interval from onset to development of stricture was 14 years, which contrasts with ulcerative colitis in which a significant proportion of strictures develop during the first attack. These anorectal strictures were of a diaphragm-like or of annular or tubular variety and resulted from transmural and submucosal inflammatory disease, perianal sepsis, and post-ileostomy atrophy. They were clearly associated with multiple complex perianal fistulae (83%), and proximal radiological narrowing or stricture (83%). There was no association with intraabdominal abscess, internal fistulae, or extraintestinal manifestations. Two of 12 patients required surgical diversion because of severe narrowing. The clinical, radiological, and pathological features of anorectal strictures occurring in Crohn's ileo-colitis have been compared with strictures occurring in other forms of inflammatory bowel disease.

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RECTAL INVOLVEMENT is the rule in ulcerative colitis, whereas in Crohn's disease of the colon the rectum is spared much more frequently, with macroscopic disease in only 40–50% of cases.[13,20,23] Microscopic disease may be present more frequently.[3] Because the rectum is of a comparatively large diameter compared to other areas of the bowel, the development of significant narrowing is relatively infrequent and true strictures rarely progress to clinically apparent obstruction.

Clinical Material

During 1944–1973, 160 patients classified as non-specific colitis, and excluding ulcerative colitis were admitted to the Ward and Private Services of the Mount Sinai Hospital. Only those patients who fulfilled our diagnostic criteria were studied. All indeterminate cases were excluded. One-hundred and sixty patients, 30 with granulomatous colitis and 130 with ileocolitis, were available for analysis. There were 12 patients with anorectal strictures (four with granulomatous colitis and eight with ileocolitis), for comparison with a control series of 148 patients.

The diagnosis of granulomatous disease was based on the criteria elaborated in detail by Lockhart-Mummery and Morson,[19] Lindner, Marshak *et al.*,[18] Korelitz *et al.*[17] and Cook and Dixon.[2] The final selection of cases was made according to the standard criteria enumerated in another publication.[12] The major features required for the diagnosis of Crohn's disease included radiological, pathological or endoscopic evidence of deep transverse fissure formation or fistulization; asymmetrical mucosal involvement; aggregated inflammatory pattern, confluent linear ulceration; discontinuity or segmental disease; right-sided involvement; rectal sparing; non-caseating epithelioid granulomas of the submucosa, skin or lymph nodes; and transmural inflammation. All indeterminate cases, and patients in whom ulcerative colitis, ischemic colitis, amebiasis, tuberculosis, and obscure malignancy could not be ruled out were excluded from this series.

The age of these 12 patients ranges 10-79 years (mean-38 years), at the time of development of stricture (Table 1). The duration from onset to development of significant stricturing was relatively long, with a mean of 14 years. The mean age at the time of onset of disease was actually 23 years, little different from the control series of 148 patients

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TABLE 1. *Age, Sex Distribution, and Duration to Stricture Formation in 12 Patients with Anorectal Strictures in Crohn's Colitis and Ileocolitis*

	Colitis	Ileocolitis	Total
Total Number in Series	30	130	160
With Stricture	4 (13%)	8 (6%)	12 (7.5%)
Without Stricture (Control)	26 (77%)	122 (94%)	148 (93%)
Male : Female	2:2	3:5	5:7
Mean Age*	25	43	14
Onset to Stricture†	7	18	14

* At the time of development of anorectal stricture.
† Mean duration from onset of disease to time of stricture formation.

in whom the mean onset age was 25 years. In patients with stricture, the disease commenced at approximately the same age as in other patients with colitis and ileocolitis, but the stricture did not develop for a period of 14 years. This relatively long period contrasts with ulcerative colitis in which 25% of strictures occur during the first attack.[5] The younger age of patients with colitis when compared with ileocolitis, and the shorter duration from onset of symptoms to stricture formation are due to the presence of two young colitis patients with a short history.

Definitions

The classification of anorectal stricture in the past has left much to be desired, and the actual size of the lesion has been very loosely defined in the many publications. The anatomy of the rectum and anus has been clearly described by numerous authors.[9,21] Strictures may be subdivided into anal and rectal groups, accepting that the rectum commences 4 cm from the anal verge, and that many strictures extend from one area to the other.

In general, rectal strictures may be subdivided into three categories depending upon the underlying pathogenic process; a diaphragmatic variety, a long tubular variety, and postileostomy "atrophy." A short diaphragmatic stricture resulting from healing ulceration may occur in ulcerative and granulomatous colitis and is not infrequent in amebic proctitis.[16]

Strictures may be further classified according to severity as mild, moderate and severe. Mild strictures are transient and respond rapidly to dilatation, and resolution of the inflammatory process. A severe stricture may be defined as one which is a major determinant of the natural history of the disease, and on occasion the indication for surgical intervention, as in two of our patients.

Results

Nine of the 12 patients had strictures which commenced ½–4 cm from the anal verge and among these were three limited to the anal canal as short diaphragmatic, fibrous strictures. The other five strictures extended into the rectum as anorectal areas of narrowing for varying distances. Three true rectal strictures commenced, 4, 5 and 7 cm above the anal verge (Fig. 1). The strictures, which were either annular (<2 cm) or tubular (>2 cm), were of varying lengths, and on occasion did extend all the way to the rectosigmoid junction, and were associated with narrowing of the distal or proximal colon (Figs. 1 and 2). The three strictures localized to the anus were narrow and would not admit more than the tip of the little finger. They may be characterized as being of the diaphragmatic variety. In the majority a sigmoidoscope could not be passed until adequate dilatation of the stricture had been accomplished. Thereafter, a pediatric sigmoidoscope could be used in some patients to assess the extent of the stricture, and evaluate disease proximal to the area of narrowing. In some the upper limit could not be clearly defined.

The symptoms and clinical characteristics of anorectal stricture have been compared with the control series of 148 patients in Tables 2a and 2b. Incontinence was found in three of the 12 patients (25%). Other clinicopathological

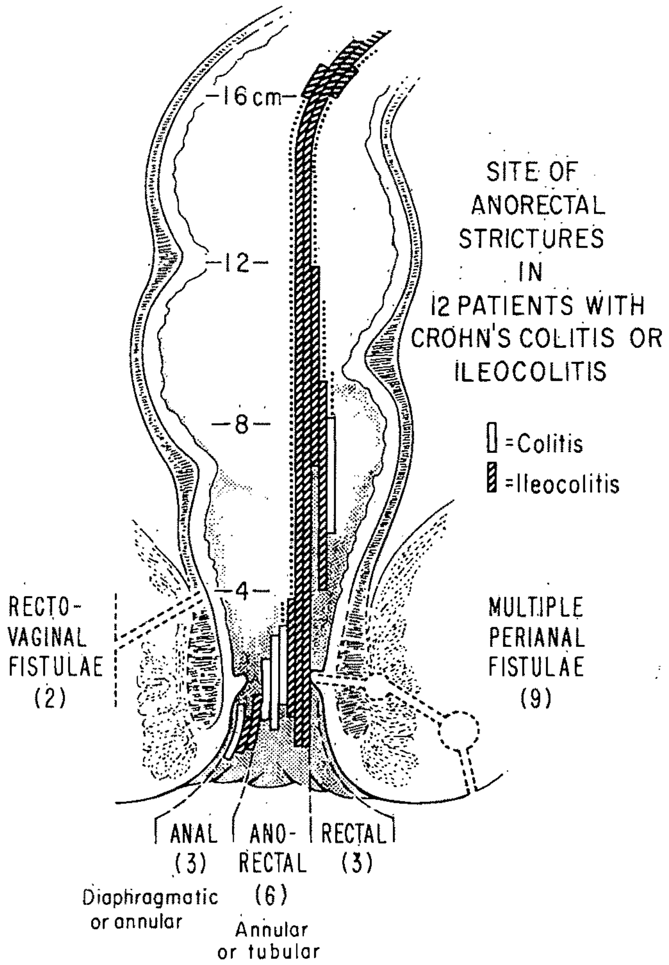
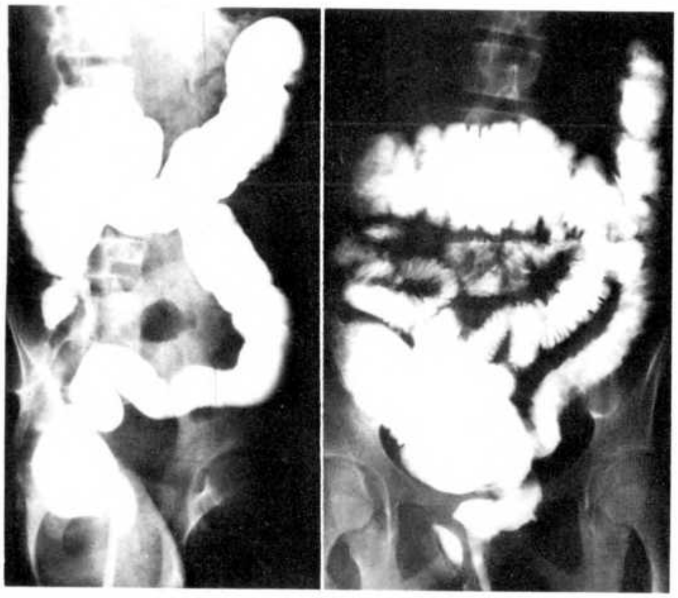


FIG. 1. Site of anorectal strictures in 12 patients with Crohn's Colitis or ileocolitis.



FIGS. 2a, b. (Left) 1966: Patient with Crohn's Ileocolitis showing ileocecal disease and minimal involvement of distal colon. (Right) 1970: Same patient following ileocolectomy with thumbprinting, cobblestoning and early fissure formation of left colon. The large perianal fistula and chronic abscess may be noted.

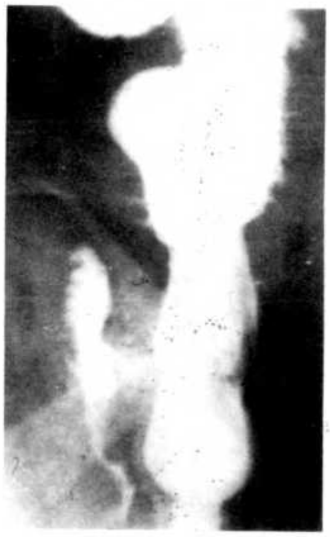


FIG. 2d. 1974: Detailed spot view taken at same time as Fig. 2C showing fistula tracts and large complex chronic perianal abscess.

and radiological features are enumerated in Table 3. The pertinent clinical features of this entity include perianal disease, associated fibrous stricture or radiological narrowing, and discontinuity of disease. Associated internal fistulae, and shortening of the bowel, occurred in five, and three patients respectively. In six of the 12 patients (50%) non-caseating granulomas were recognizable histologically. Other features noted in Table 3, are, anemia in 11 patients, and extraintestinal manifestations in seven patients.

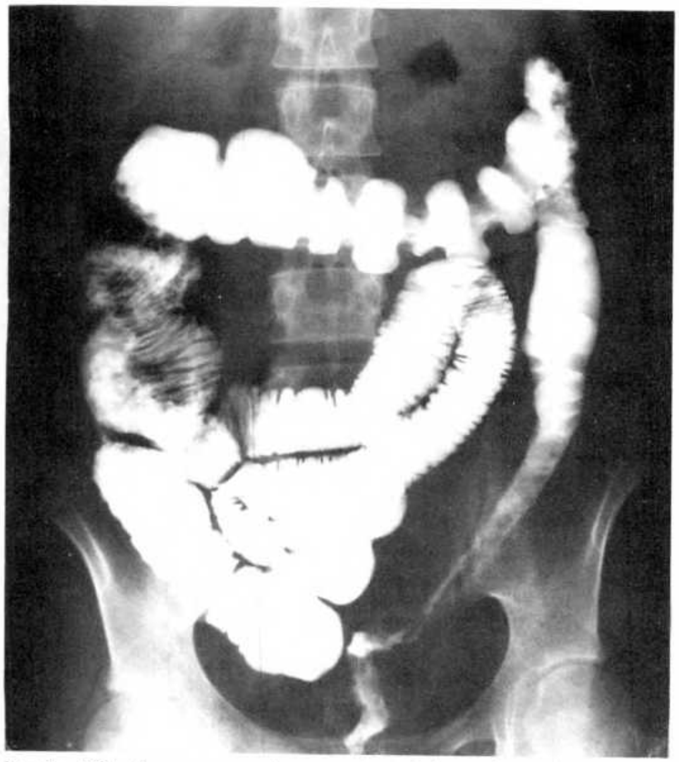


FIG. 2c. 1974: Shows progressive narrowing of descending colon, sigmoid, and rectum, with recurrent ileal disease proximal to the anastomosis.

There was a clear association with fibrous strictures or radiological narrowing in the other areas of the gastrointestinal tract. Thus stricture or radiologic narrowing was found at other sites in 10 of 12 cases (83%) (Fig. 2c and Table 4) with anorectal stricture. This was significantly different from the control series in which radiological narrowing or stricture at sites other than the rectum occurred in 41 of 148 patients or 28% ($X^2 = 13.36$, $DF = 1$, $P = <0.001$). There was in addition significant shortening of the colon due to cicatrising contraction in at least four patients. In other patients with fairly extensive involvement, shortening did not occur because of intervening normal areas.

Perianal abscesses and fistulae were characteristically associated with anorectal stricturing, and were found in 10 patients (Figs. 2b and 2d). Of the two without this feature, one had a solitary hemorrhoidal tag and only one was completely free of any perianal or perirectal involvement. Perianal disease is characteristic of Crohn's colitis with anorectal stricture formation, and shows a statistically significant difference from the incidence in the control series ($P = <0.05$). When present, perianal disease is multiple, complex, recurring, and chronic (Fig. 2b-d). It is also a feature of lymphogranuloma venereum but not of amoebic strictures.[16]

Discussion

Non-malignant strictures may occur in inflammatory disease of the bowel involving colon. With the growing recognition of vascular disease involving the bowel, rectal strictures have been described following vascular ischemia

TABLE 2a. *Clinical Features of 12 Patients With Rectal Strictures in Crohn's Colitis and Ileocolitis*

	Colitis	Ileocolitis	Total
Total Number of Patients	4	8	12
Perianal Disease	4	7	11 (92%)
Toxemia/Fever	3	7	10 (83%)
Diarrhea	2	7	9 (75%)
Weight Loss	3	6	9 (75%)
Abdominal Pain	2	5	7 (58%)
Abdominal Tenderness	1	6	7 (58%)
Peripheral, Systemic	3	4	7 (58%)
Fistulae, Internal	1	4	5 (42%)
Sub-acute Obstruction	1	4	5 (42%)
Overt Bleeding	3	1	4 (33%)
Abdominal Mass	—	4	4 (33%)
Intro-abdominal Abscess	—	3	3 (25%)
Incontinence	1	2	3 (25%)

TABLE 2b. *A Comparison of the Percentage Incidence of Clinical Features in 12 Patients With Rectal Strictures and a Control Series of 148 Patients With Crohn's Colitis and Ileocolitis*

	Stricture	Control
Total Number of Patients	12	148
Perianal Disease	92%	53%*
Toxemia/Fever	83%	65%
Diarrhea	75%	95%
Weight Loss	75%	72%
Abdominal Pain	58%	89%
Abdominal Tenderness	58%	48%
Peripheral, Systemic	58%	48%
Fistulae, Internal	42%	39%
Sub-acute Obstruction	42%	33%
Overt Bleeding	33%	31%
Abdominal Mass	33%	27%
Intra-abdominal Abscess	25%	22%

* Statistically significant Difference: $X^2 = 5.3$ D.F. = 1 P = <0.05

of the more chronic variety, usually associated with sigmoid involvement.[1,4,7,24]

To clarify the various inflammatory and ischemic processes leading to benign anorectal stricture, we have tabulated various aspects of the epidemiology, character of the stricture, and associated extraintestinal, radiological and pathological findings in five conditions found to be associated with such strictures (Table 7). Most of these inflammatory processes tend to occur in young adults. The exception is the ischemic stricture which occurs in elderly patients associated with ischemic vascular disease elsewhere in the body, and occasionally following inferior mesenteric artery occlusion.[25]

The long tubular stricture, characteristic of lymphogranuloma venereum and found in recent cases of ischemic proctitis, may also be found with granulomatous colitis. In two patients, the stricture extended from the anus to descending colon (Fig. 2c). This type is associated either with extensive perianal disease, or with an extensive rectal submucosal inflammatory process which may extend up to the rectosigmoid or even to involve the whole bowel in the process of narrowing and shortening.

Ulcerative colitis, which almost always involves the rectum, with or without synchronous or metachronous proximal colonic disease may result in rectal stricture on occasion. Colonic strictures are not infrequent, occurring in 2–5% of patients, with disease at any particular site in the colon.[5] These authors find a somewhat higher incidence (7.8%) in the rectal region. The incidence in various series varied from 4–9%.[5,6,11,15,18] In one series from the Mayo Clinic,[22] the postileostomy patients with diversion of the fecal stream were found to have anorectal strictures in 47% of cases! These strictures, which may on occasion occur with the first attack of ulcerative colitis, usually develop in the chronic continuous form of disease,[6] and are associated with either healing ulceration or extensive inflammatory sclerosis.

When strictures involve the colon, there is a clearly defined as pathogenetic difference between strictures in ulcerative as opposed to Crohn's colitis. This has been recognized in a recent paper by Goulston and McGovern.[10] Whereas in Crohn's colitis progressive fibrous stricture results from the "Cicatrising" inflammatory process, in ulcerative colitis, the major thickening occurs in the muscle layers particularly the muscularis mucosae; the muscle contraction and hypertrophy contribute to the strictures which develop. Even in ulcerative colitis, malignant strictures, al-

TABLE 3. *Distinguishing Features of 12 Patients With Anorectal Strictures Due to Crohn's Colitis and Ileocolitis*

I.	Perianal Disease	
	Abscesses and Fistulae	10*
	Hemorrhoidal Tag Only	1
II.	Intestinal Complications	
	Associated Stricture	10
	Associated Fistulae	5
	Abscesses†	4
	Toxic Dilatation	1
III.	Extra-intestinal Manifestations‡	
	Skin	5
	Joint	2
	Liver	1
	Duodenal Ulcer	1
	Amyloid	1
	Eye	1
	Malabsorption, osteoporosis	1
IV.	Hematological	
	Anemia	11
V.	Radiological	
	Discontinuity	11
	Assymmetry	7
	Cobblestone	7
VI.	Pathological	
	Non-caseating Granulomas	6

* Multiple complex perianal and ischio-rectal abscess and fistulae.
† Intra-abdominal or retro-peritoneal.
‡ 7 Patients—some with multiple extra-intestinal manifestations.

though occurring on occasion, are the exception rather than the rule.[9]

The specific infective diseases, amebiasis and lymphogranuloma venereum occur most frequently in the tropics and subtropical regions, but with expanding world travel will doubtless be seen more frequently in northern Europe, Britain and America. Non-specific ulcerative colitis, Crohn's colitis and ischemic colitis, on the other hand, are already relatively common diseases in America, Britain and the Scandinavian Countries.

The anatomic pattern and distribution of these diseases is usually characteristic. Ulcerative colitis and lymphogranuloma venereum start distally, with proximal extension of the disease. Lymphogranuloma venereum may extend to the sigmoid, and ulcerative colitis may spread to involve the entire colon. By contrast, ischemic disease usually affects predominantly the splenic flexure and less frequently the sigmoid, while Crohn's disease and amoebic colitis are predominantly right-sided diseases. Discontinuity of disease is characteristic of granulomatous disease (Fig. 2a-d).

The natural history of anorectal stricture in Crohn's disease involving the colon is generally that of a self-limited narrowing, or fibrous stricture which responds to finger or instrumental dilatation and ceases to be a problem if the major related factor, the complex perianal fistulae is treated and controlled. This was the course in four of the patients, particularly those in whom the narrowing was confined to the anal canal and relatively short in length.

Of the longer low anorectal strictures, three required repeated dilatation. Of these patients, at least one is undergoing regular dilatation at the present time, and may ultimately require surgical intervention.

In one patient toxic dilatation developed proximal to the stricture which narrowed progressively following proximal diverting ileostomy. Because of extensive perianal disease and subsequent fibrosis with progressive postiliectomy stricturing reconstitution of gastrointestinal continuity could not be carried out.

In two patients stricturing associated with rectal disease proximally resulted in the development of a rectovaginal fistula. One required no further treatment apart from medical measures to control the disease. The other patient, however, eventually came to subtotal colectomy, and ileostomy for extensive perianal disease, rectovaginal fistulae, and tight rectal stricture. One patient with extensive stricturing from anus to involve almost all of the colon was advised total proctocolectomy, but this was not carried out as the patient was too old and too ill. One patient came to major surgery following successful resolution of the inflammatory disease following right hemicolectomy. The perianal inflammatory disease and the rectal stricture subsided. Complex and extensive perianal disease requires incision and drainage on occasion, but should be treated conservatively whenever possible because of the difficulty in obtaining satisfactory surgical healing.

TABLE 4. *Sites of Associated Stricture or Radiological Narrowing in 10[*] of 12 patients with Anorectal Strictures*

Terminal Ileum	6[**]
Ascending Colon	2
Transverse Colon	1
Splenic Flexure	3
Descending Colon	3
Sigmoid Colon	3
Rectosigmoid	4
Anorectum	12

[*] Includes three patients with multiple strictures and one with narrowing of distal small bowel and all of large bowel.

[†] Multiple ileal strictures in two patients.

TABLE 5. *Associated Fistulae in 5 of 12 Patients with Anorectal Strictures*

Rectovaginal	2
Sigmoidoduodenal	1
Ileocecal	1
Ileosigmoid	1
Colocavitory	1
Ileomesenteric (multiple)	1

Conclusions

Anorectal stricture occurred in 12 of 160 patients (7.5%) with Crohn's disease involving the colon. These strictures, although benign, constitute a major clinical problem, and will often resolve with control of the frequently associated perianal inflammatory process.

In approximately half of the involved cases rectal narrowing may lead to partial or complete obstruction of a significant degree. In this series of 12 cases, four were mild, four moderate and four severe.

In contrast to a localized process such as lymphogranuloma venereum, rectal stricture in granulomatous disease should be considered as part of the total disease picture and may be associated with perianal disease, rectovaginal fistulae, proximal stricturing in the bowel, and activity of the Crohn's disease elsewhere in the gastrointestinal tract and throughout the body. Although rarely a major determining factor in the course of the disease, on occasion such a stricture can determine the treatment to be carried out, and necessitate surgical intervention.

TABLE 6. *Operative Procedures in 12 Patients With Anorectal Strictures in Crohn's Colitis and Ileocolitis*

Non-operative		3
Surgical		9
I.	Dilatation of Rectal Stricture	3
II.	Incision & Drainage of Intra-abdominal Abscess	3
III.	Ileostomy[*]	2
IV.	Colostomy Diverting + Closure of Colostomy	1
V.	Ileocolostomy[†]	4
VI.	Bypass	2
VII.	Resection: Ileocolic Resection	2
	Subtotal Colectomy	1
VIII.	Appendectomy	2

[*] Diverting 1 complementary to subtotal colectomy

[†] 2 with bypass 2 with resection

TABLE 7. *Features of Rectal Stricture Occuring in Inflammatory and Vascular Disease of the Colon*

Age	Crohn's 30–50	Ulcerative 20–40	Ischemic 50–70	Amebic 16–40	Lymph. Venereum 20–60
Epidemiology	UK, USA, Sweden etc.	UK, USA, Sweden etc.	USA & Europe etc.	South Africa Tropics etc.	West Indies Tropics etc.
Incidence of Strictures	11%	5–8%	0–6%	0–5%	25–45%
Major Site of Disease	Ileum & rt. colon	Rectum & lt. Colon	Spl. flex & sig. col	Cecum	Rectum & sig. Colon
Assoc. Perianal Disease	80%	5–7%	none	none	frequent
Assoc. Stricture of Bowel	80%	5–10%	occasionally sig. & splenic flexure	occasional cecum and rectum	occasionally up to splenic flexure
Type of Stricture	diaphragmatic, tubular, annular	diaphragmatic, tubular, annular	tubular	diaphragmatic, acute tubular, annular	tubular usually to sigmoid
Site of Stricture	Anorectum 1–5 cm from anal verge	anorectum	midrectum	low rectum	anorectum 3–5 cm from anal verge
Assoc. Internal Fistula	common (50%)	rare except recto-vaginal	none	rare	none
Extra-intestinal Manifestations	frequent (50%)	frequent	ischemic disease elsewhere	amebic hepatitis	none
Radiology	fissures, deep ulcers, fistulae, discontinuity	shallow ulcers in continuity	thumb-printing sacculation, tubular narrowing	ameboma with tubular stricture	long tubular stricture, saw tooth or smooth edge, perianal fistula
Histopathology	sarcoid reaction, transmural disease	mucosal disease, crypt abscesses	fibrosis, hemosiderin laden macrophages, vas. lesion	ameba, ameboma, acute & chronic inflammation	granulation tissue, plasma cells, lymph's
Course	relapsing	relapsing, tendency to carcinoma	acute self limited	progressive	progresive with obstruction
Treatment	Azulf. steroids, dilatation, surgery	azulf. dilatation, surgery	conservative	emetine, chloroquine	antibiotics tetracycline

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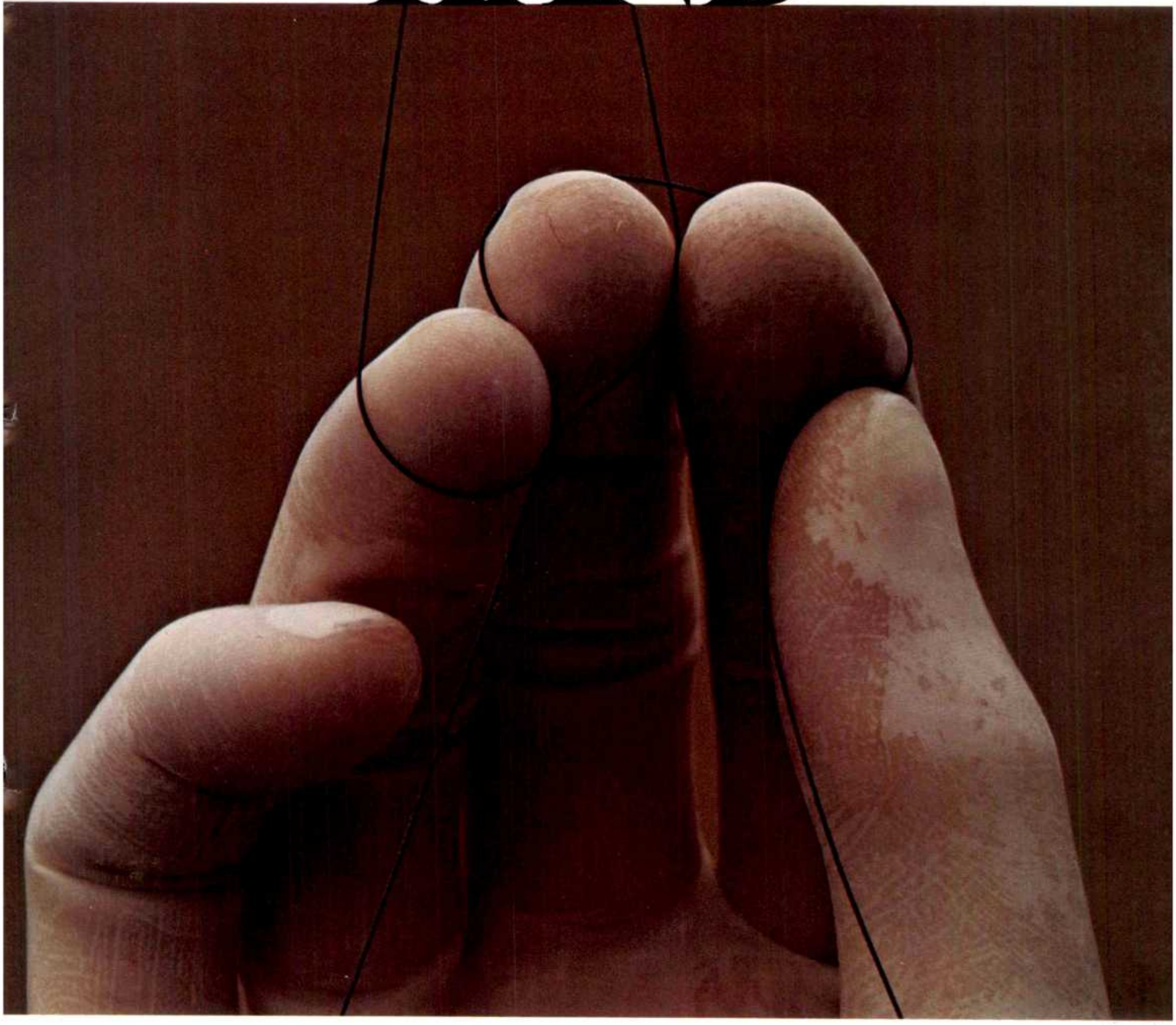
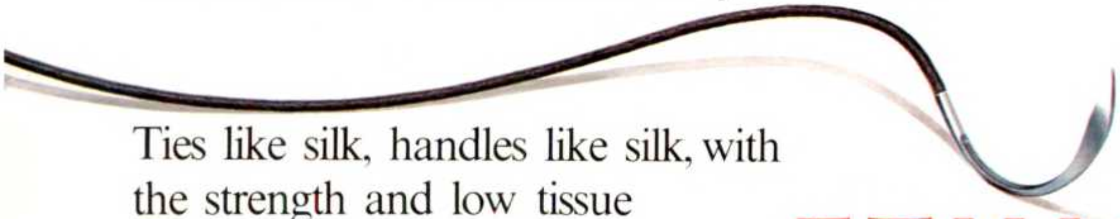
HAND



The fine handling qualities of silk are in your hands with NUROLON* Black Braided Nylon Suture.



Ties like silk, handles like silk, with the strength and low tissue reactivity of a synthetic.

ETHICON

*Trademark

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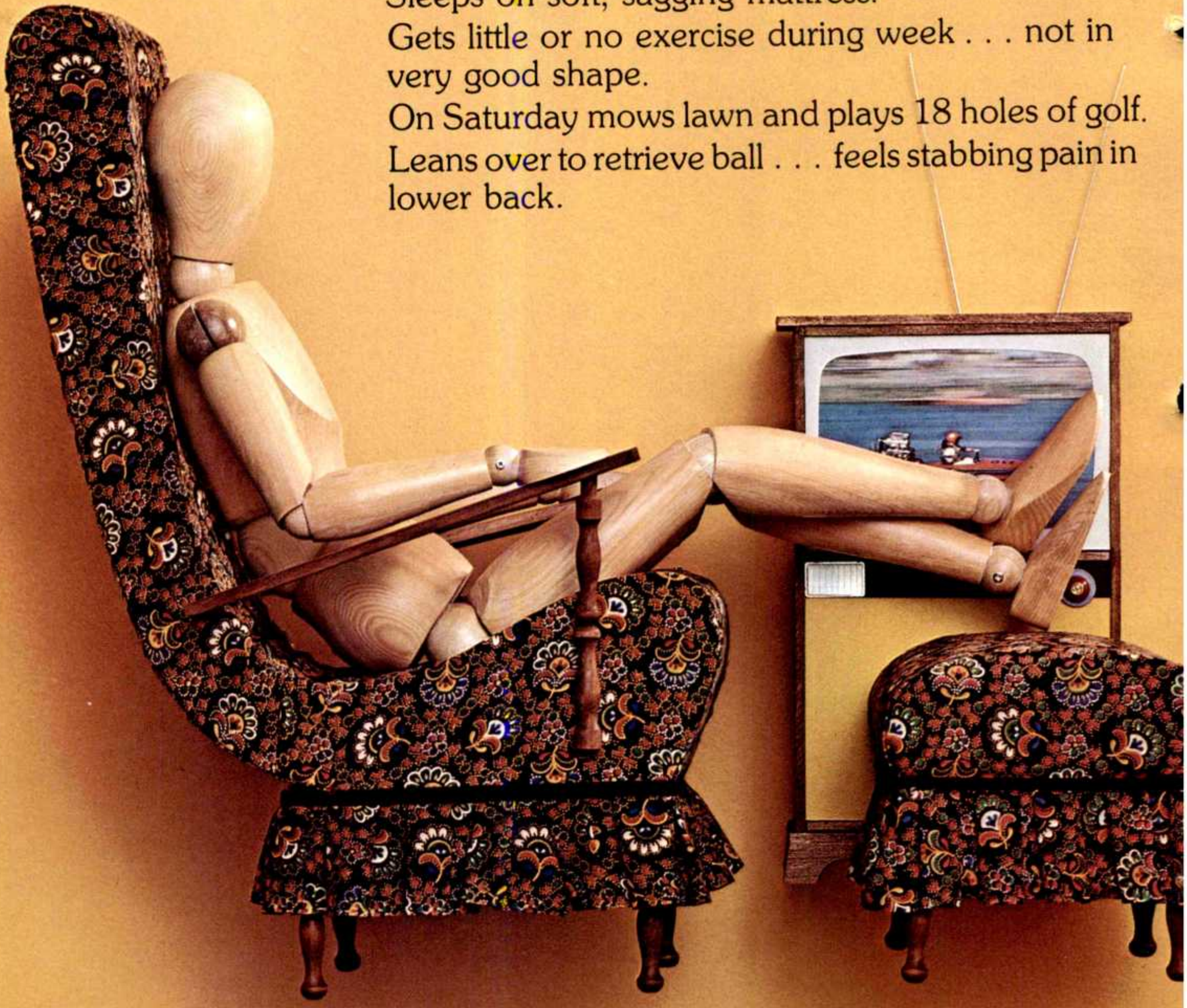
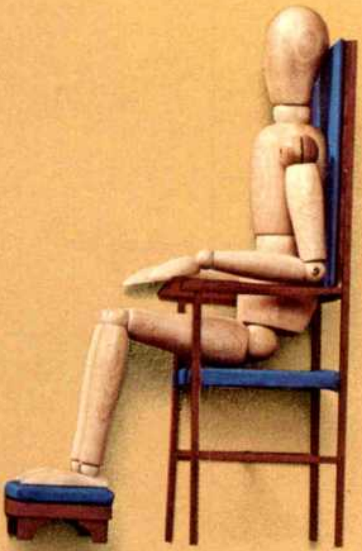
the low-back patient and his problems:

SOFT LIFE 'SUBURBANITE' BACKACHE

Sedentary job. Sits most of day in plush swivel chair.
Sits slumped in overstuffed furniture at home.
Sleeps on soft, sagging mattress.
Gets little or no exercise during week . . . not in very good shape.
On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in lower back.



the solution:



At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in overstuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

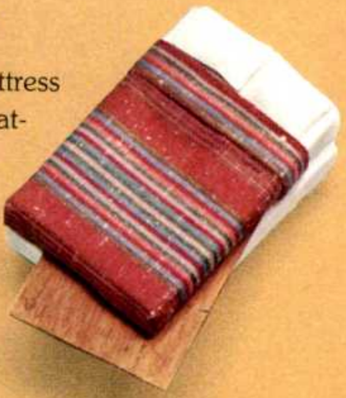
ROBAXIN®-750

brand of

methocarbamol 750 mg. capsule-shaped tablets

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾" thick between mattress and box springs. The use of moist heat is often very beneficial.



Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

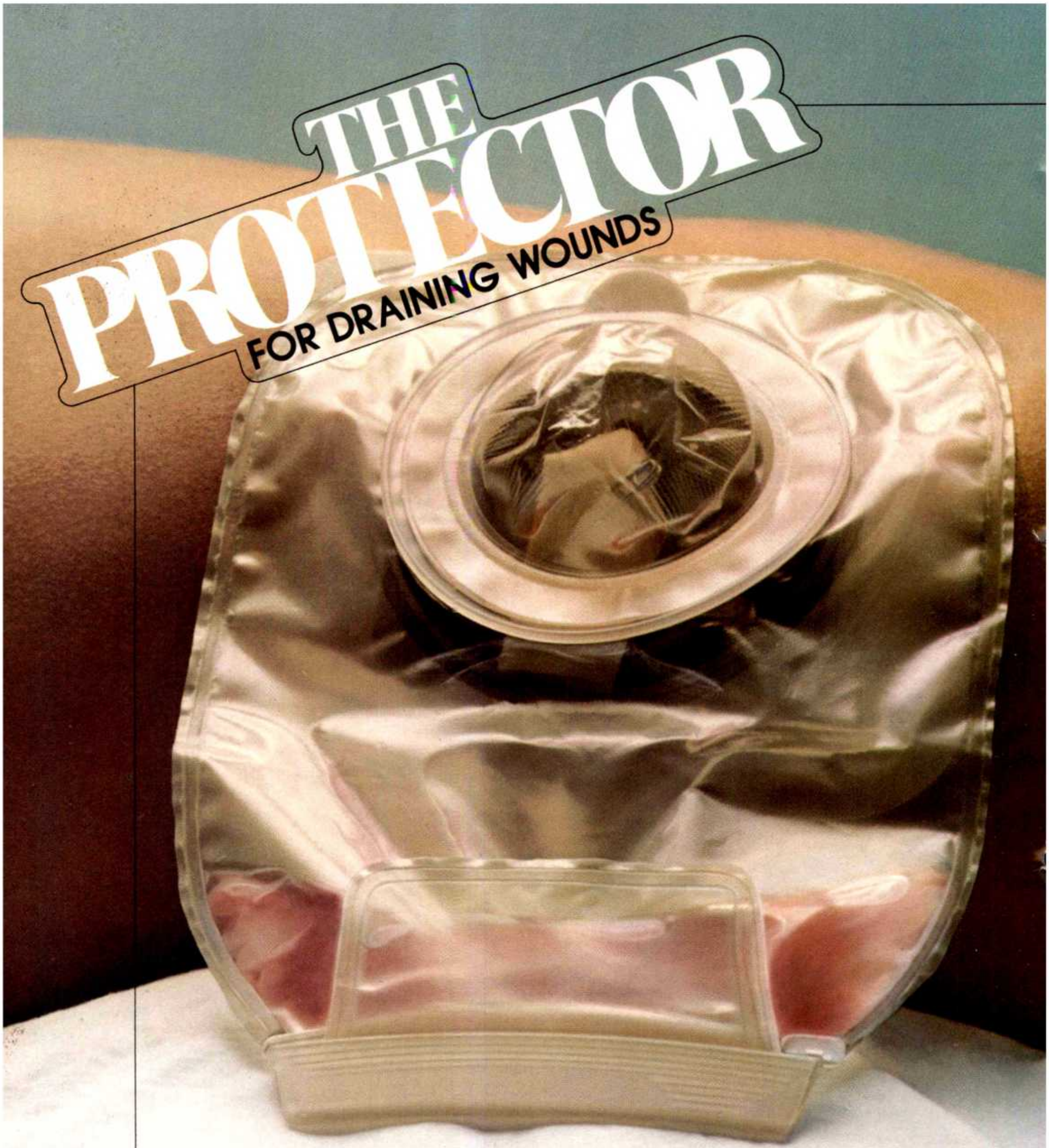
Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

A. H. Robins Company, Richmond, Va. 23220
A·H·ROBINS



MORE CONVENIENCE FOR YOUR SURGICAL TEAM... MORE COMFORT FOR YOUR PATIENT

The Hollister Draining-Wound Management System can be applied in the O.R. or in your patient's room, to make post-operative care simpler and more protective for everyone.

There are no wet, messy dressings to touch. And the wound site doesn't require a dressings change every time it's inspected.

Your patient is not subject to painful stripping of skin and damage to regenerating tissue. Contamination from outside sources is reduced to a minimum. And your patient can now become ambulatory with greater ease and comfort.

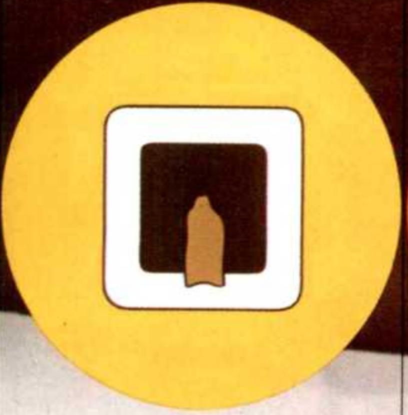
For you and your patient, this new Hollister Draining-Wound Management System is truly the better alternative.

NOW A BETTER ALTERNATIVE TO ABSORBENT DRESSINGS AFTER STOMACH, LIVER, PANCREAS, GALLBLADDER, KIDNEY, AND OTHER SURGICAL PROCEDURES AS WELL AS TRAUMATIC AND FISTULAR WOUNDS.

Introducing the HOLLISTER DRAINING-WOUND MANAGEMENT SYSTEM

Keeps Fluids Away From Patient's Skin and Guards Against Irritation and Contamination.

Protect skin with a Karaya Blanket around the wound site.

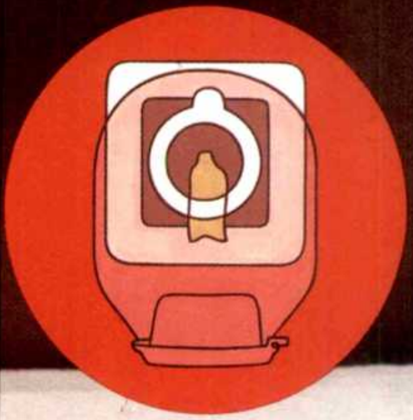


Snug fit of Karaya blanket around draining wound directs discharge into collection bag. Helps prevent pooling at wound site.

Collect exudate in a Drainage Bag that keeps fluid away from the wound.

Secretions are trapped inside a collector made of odor-barrier film. Exudate is visible—and available for accurate measurement.

Inspect wound through Access Cap without the trauma of dressing removal.



Translucent "window to the wound" permits observation and easy access for drain tube adjustment.

ALL ELEMENTS IN THE SYSTEM—INCLUDING THE KARAYA BLANKET—ARE STERILE-PACKED.

Write for more information and professional samples.

HOLLISTER

HOLLISTER, INC., 211 E. CHICAGO AVE., CHICAGO, ILL. 60611

Manufacturer of Ostomy and Urinary Collection Products.

In serious respiratory tract infections*

*due to susceptible microorganisms

ANCEF® IV meets the challenge

- **With 93% efficacy in respiratory tract infections.**
  In clinical trials, 'Ancef' produced good or excellent responses* in 93% of 377 patients with respiratory tract infections due to susceptible organisms (See Indications section of brief summary for list of organisms).
- **With high and prolonged serum levels.**
  Following single 1 gram IV injections in healthy adult volunteers, 'Ancef' produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.
- **With a low risk of phlebitis at the IV injection site.**
  Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. These data were derived from pre-marketing clinical studies in small populations. While further clinical experience may reveal a greater incidence of adverse effects, it should be noted that the incidence of known phlebitis has not increased with over a year's clinical experience since introduction.
- **With no reported nephrotoxicity.**
  (Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without evidence of renal or hepatic impairment.)
- **With the flexibility of IV or IM administration.**

Adverse Reactions

Adverse reactions reported in clinical trials included pain on injection, rash, G.I. symptoms, pruritus, and phlebitis. For a complete list of adverse reactions reported with 'Ancef' therapy, please see next page.

Warning: In penicillin-allergic patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity.

*(Excellent response: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good response: Initial improvement at 2-4 days with maximum improvement between 4-10 days. Results collected from identical clinical protocols.)

See next page for a brief summary of the prescribing information.

ANCEF®

brand of

STERILE

CEFAZOLIN SODIUM

Injection: 250 mg, 500 mg and 1 gram vials

meets the challenge, IV or IM

ANCEF®

brand of

STERILE CEFAZOLIN SODIUM

meets the challenge, IV or IM

Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant)

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae (formerly *D. pneumoniae)*
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus *(P. vulgaris, P. morgani, P. rettgeri)* are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae), Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef.'

CONTRAINDICATIONS

'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram+ cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

HOW SUPPLIED

Ancef® (sterile cefazolin sodium, SK&F)—supplied in vials equivalent to 250 mg., 500 mg., and 1 gram of cefazolin.

Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, PA 19101

The most up-to-date volume on surgical science and practice...

SESAP II IS:

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A completely new program, it reflects the results of a three-year effort by 70 nationally recognized authorities.

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The 750 items comprising SESAP II emphasize information of value to your daily practice.

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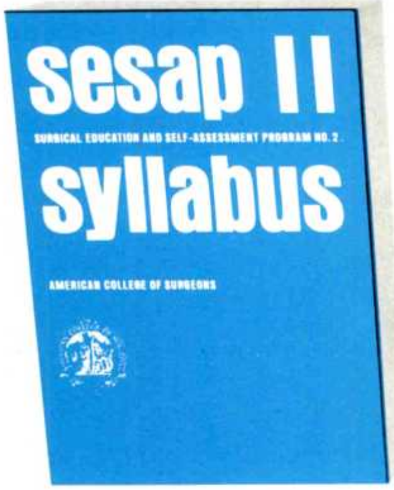
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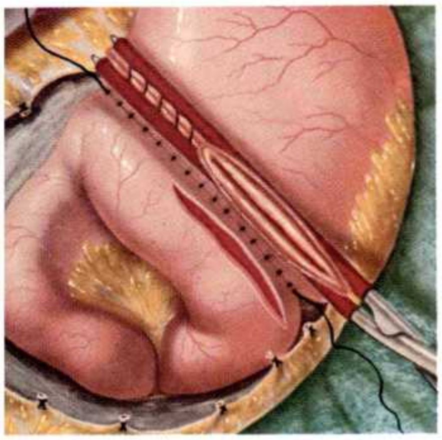
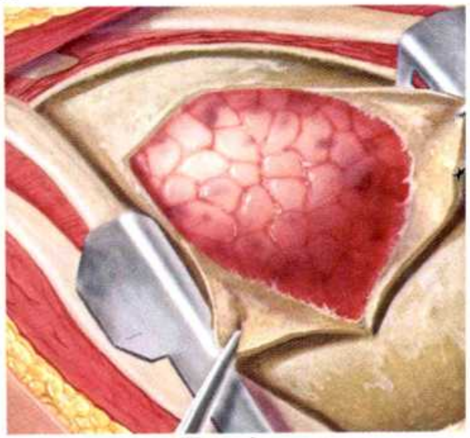
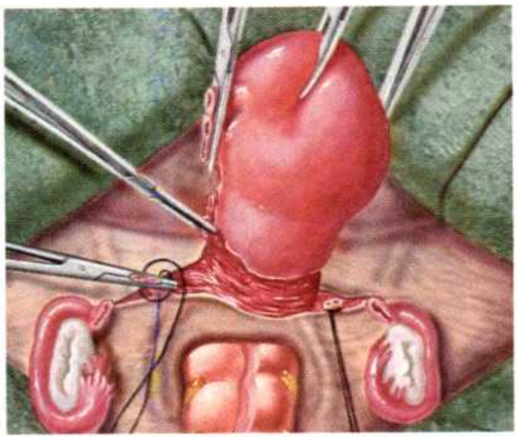
An unextreme parenteral analgesic can be preferable for the relief of moderate to severe pain associated with many everyday hospital situations.


Gastrectomy

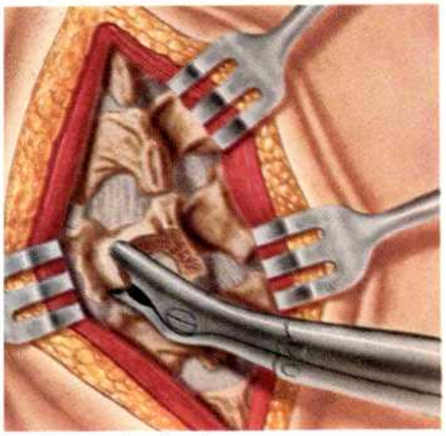
Ureteral colic


Thoracic surgery

Traumatic pain


Hysterectomy

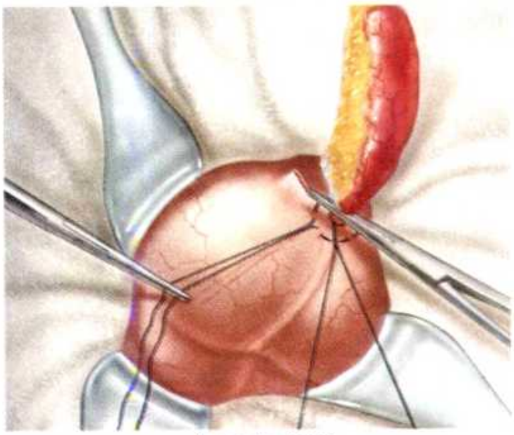
Endoscopy


Laminectomy

Burns

Multiple fractures

Acute bursitis


Appendectomy

Intestinal colic

Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

the unextreme injectable for serious pain

Talwin doesn't go to extremes.

Yet, Talwin relieves serious pain (moderate to severe pain) in the great majority of everyday hospital situations.

For most serious pain – Talwin has in fact been shown comparable to narcotics such as morphine and meperidine, in analgesic efficacy... with less likelihood of some of the extreme adverse effects produced by the opiates in general.

With Talwin there is a low incidence of respiratory depression, hypotension, urinary retention, and constipation.

In moderate to severe pain

Injectable **Talwin®**

brand of **pentazocine**
(as lactate)

extremely effective for most patients

30 mg. 45 mg. 60 mg.

See important product information concerning warnings, adverse reactions, patient selection, prescribing and precautionary recommendations on last page of this advertisement.

Talwin®
Brand of **pentazocine** (as lactate)
Analgesic for Parenteral Use

Ampuls: 30 mg. (1 ml.), 45 mg. (1½ ml.), and 60 mg. (2 ml.)
Vials: (10 ml.) 30 mg./ml.
30 mg. for I.V., I.M., or S.C. use
45 mg. for I.M. or S.C. use
60 mg. for I.M. or S.C. use

Indications: For the relief of moderate to severe pain. Talwin may also be used for preoperative or preanesthetic medication and as a supplement to surgical anesthesia.

Contraindication: Talwin should not be administered to patients who are hypersensitive to it.

Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain. Just as with all medication, the oral form of Talwin is preferable for chronic administration.

Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

How Supplied: *Uni-Amp*T.M.*—Individual unit dose ampuls of 1 ml. (30 mg.) and 2 ml. (60 mg.)* in boxes of 25.

Ampuls of 1½ ml. (45 mg.) in boxes of 10, 25, and 100.

Each 1 ml. contains Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base and 2.8 mg. sodium chloride, in water for injection.

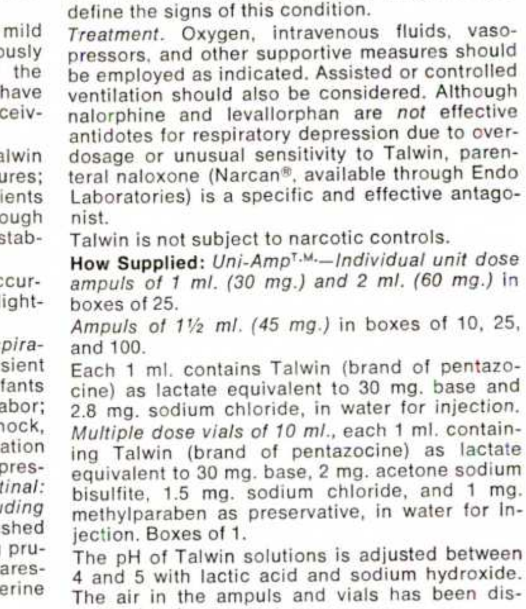
Multiple dose vials of 10 ml., each 1 ml. containing Talwin (brand of pentazocine) as lactate equivalent to 30 mg. base, 2 mg. acetone sodium bisulfite, 1.5 mg. sodium chloride, and 1 mg. methylparaben as preservative, in water for injection. Boxes of 1.

The pH of Talwin solutions is adjusted between 4 and 5 with lactic acid and sodium hydroxide. The air in the ampuls and vials has been displaced by nitrogen gas.

Winthrop Laboratories, New York, N.Y. 10016

Winthrop

(1639M)



the unextreme injectable for serious pain

Injectable
Talwin®
brand of
pentazocine
(as lactate)

Vacu-Drain

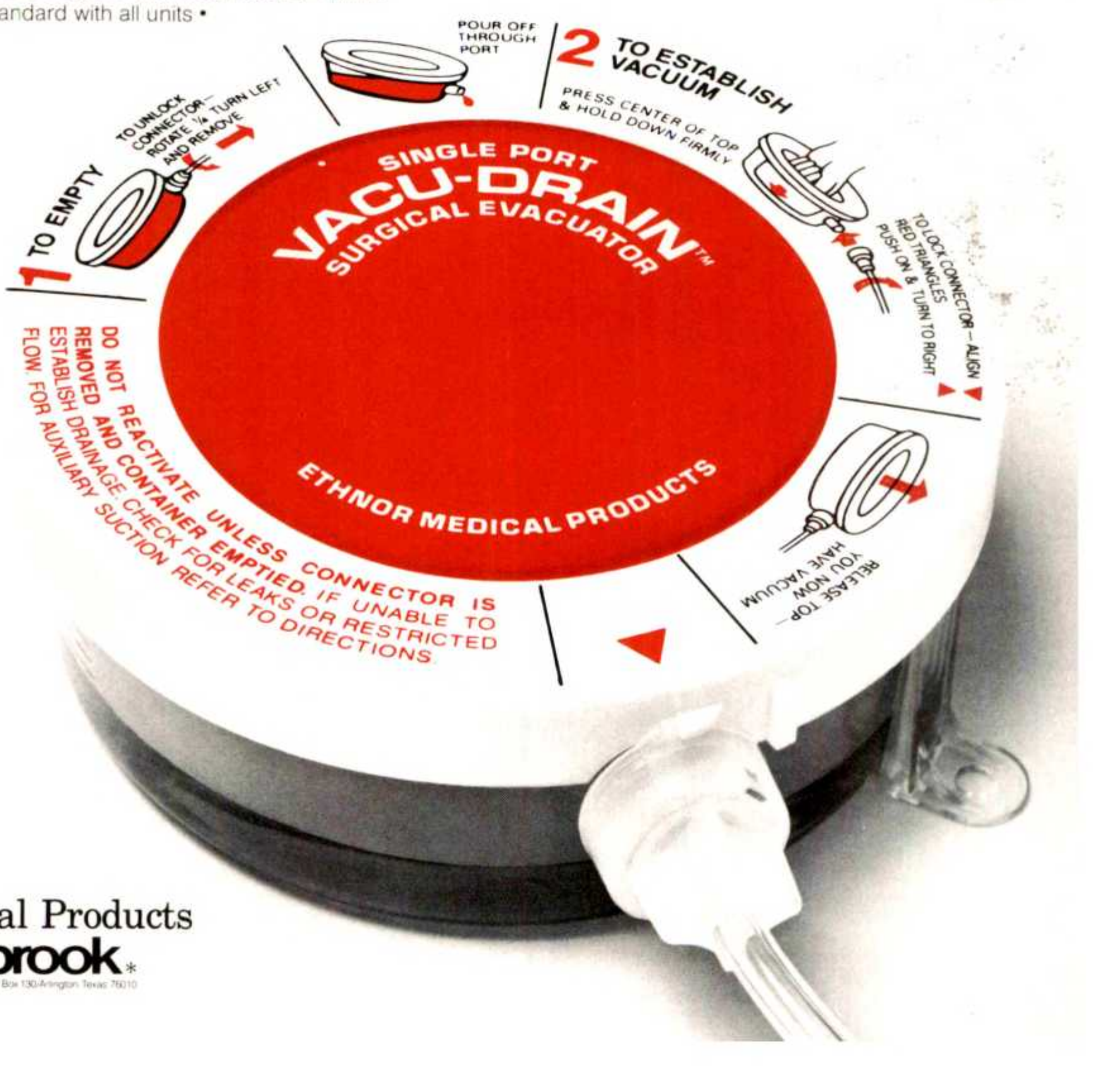
Trademark

Single-port surgical evacuator

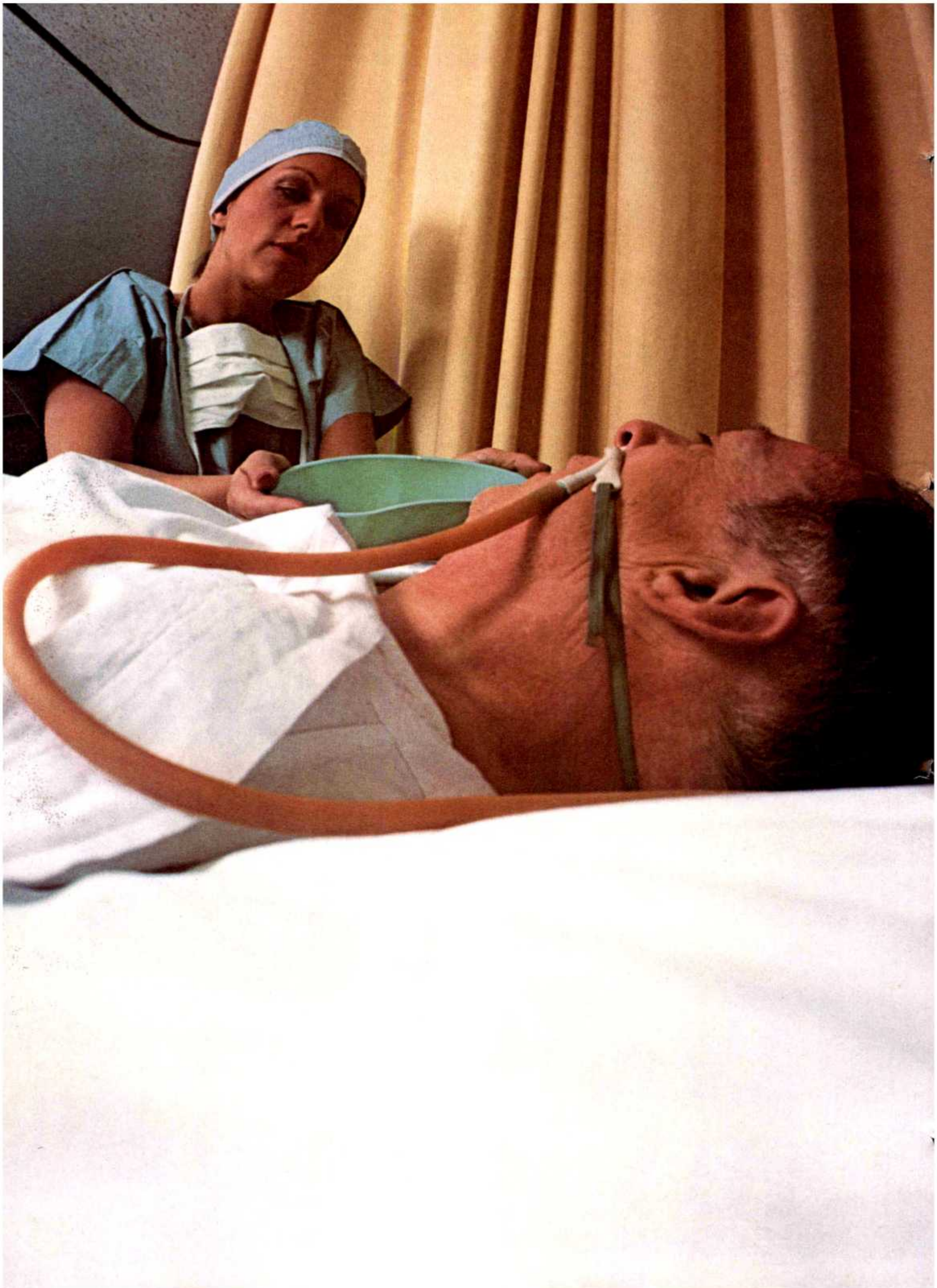
for convenient closed wound suction

The VACU-DRAIN single-port surgical evacuator is simple for the O.R. staff to activate, easy for the floor nurse to empty and maintain. The latex membrane provides a gentle, reproducible vacuum through the suction cycle, reducing the tendency to clog. The canister is of a rigid design, not subject to accidental compression, so there is little chance of backflow.

The VACU-DRAIN surgical evacuator system includes:
• 400 ml. capacity single-port container with fluid level calibrations • Unique twist-lock connector • Exclusive no-cut adapter for single or double wound drainage • The VACU-DRAIN system is available with medium (1/8") or large (1/4") perforated wound tubing with or without needle • In-line auxiliary suction adapter is standard with all units •


1 TO EMPTY
TO UNLOCK CONNECTOR— ROTATE ¼ TURN LEFT AND REMOVE
POUR OFF THROUGH PORT
2 TO ESTABLISH VACUUM
PRESS CENTER OF TOP & HOLD DOWN FIRMLY
TO LOCK CONNECTOR — ALIGN RED TRIANGLES PUSH ON & TURN TO RIGHT
RELEASE TOP— YOU NOW HAVE VACUUM
SINGLE PORT
VACU-DRAIN™
SURGICAL EVACUATOR
ETHNOR MEDICAL PRODUCTS
DO NOT REACTIVATE UNLESS CONNECTOR IS REMOVED AND CONTAINER EMPTIED. IF UNABLE TO ESTABLISH DRAINAGE CHECK FOR LEAKS OR RESTRICTED FLOW. FOR AUXILIARY SUCTION REFER TO DIRECTIONS.

ETHNOR Medical Products
available through **Arbrook***
Arbrook Inc. P.O. Box 130/Arlington, Texas 76010



A phenothiazine is preferred...

when drug treatment is indicated in postoperative vomiting.[1]

'Compazine' offers:

- unsurpassed antiemetic activity
- rapid patient response
- four dosage forms and strengths for postoperative vomiting

'Compazine' is contraindicated in pediatric surgery and in greatly depressed states due to C.N.S. depressants.

The possibility of postoperative aspiration of vomitus should be borne in mind.

1. The Medical Letter, 16(11):48 (May 24) 1974.

Before prescribing, see complete prescribing information in SK&F literature or PDR. The following is a brief summary.

Indications: To control severe nausea and vomiting.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants; bone marrow depression; pediatric surgery.

Warnings: Avoid using in patients hypersensitive (e.g., blood dyscrasias or jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery) especially during the first few days' therapy. Prochlorperazine may intensify or prolong the action of other C.N.S. depressants. Not recommended for children under 20 pounds or 2 years of age.

Use in pregnancy only when potential benefits outweigh hazards.

Precautions: Antiemetic effect may mask toxic drug overdosage or physical disorders. Postoperative aspiration of vomitus has occurred in a few surgical patients who received prochlorperazine as an antiemetic. Deep sleep and coma have been reported, usually with overdosage. **In children with acute illnesses or dehydration, use only under close supervision.**

Adverse Reactions: Drowsiness, dizziness, amenorrhea, blurred vision, skin reactions. Hypotension. Cholestatic jaundice, leukopenia, agranulocytosis. Fatty changes in the liver have been observed in a few patients who died while receiving the drug (no causal relationship has been established). Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, persistent tardive dyskinesia. Contact dermatitis is a possibility with concentrate and injectable forms.

Other adverse reactions reported with Compazine (prochlorperazine, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., severe hypotension in mitral insufficiency or pheochromocytoma).

Grand mal convulsions; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat and organophosphorus insecticides; dryness of mouth, nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, inhibition of ejaculation; reactivation of psychotic processes, catatonic-like states; hypotension (sometimes fatal); cardiac arrest; pancytopenia, thrombocytopenic purpura, eosinophilia; biliary stasis; lactation, galactorrhea, gynecomastia, menstrual irregularities, false-positive pregnancy tests; photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis; asthma, laryngeal edema; angioneurotic edema, anaphylactoid reactions; peripheral edema; reversed epinephrine effect; hyperpyrexia; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits.

EKG changes have been reported, but relationship to myocardial damage is not confirmed. Discontinue long-term, high-dose therapy gradually.

NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported, but no causal relationship has been established.

Supplied: Tablets—5, 10 and 25 mg., in bottles of 100; Spansule® capsules—10, 15, 30 and 75 mg., in bottles of 50; Injection—5 mg./ml.; Suppositories—2-1/2, 5 and 25 mg.; Syrup—5 mg./5 ml.; Concentrate (intended for institutional use only)—10 mg./ml.; Single Unit Packages of 100 (intended for institutional use only)—5 and 10 mg. tablets; 10, 15 and 30 mg. 'Spansule' capsules.

Compazine®
brand of
prochlorperazine

Injection: 5 mg./ml.

rapid ▪ reliable ▪ effective

Smith Kline & French Laboratories SK&F
Division of SmithKline Corporation, Philadelphia, Pa. 19101

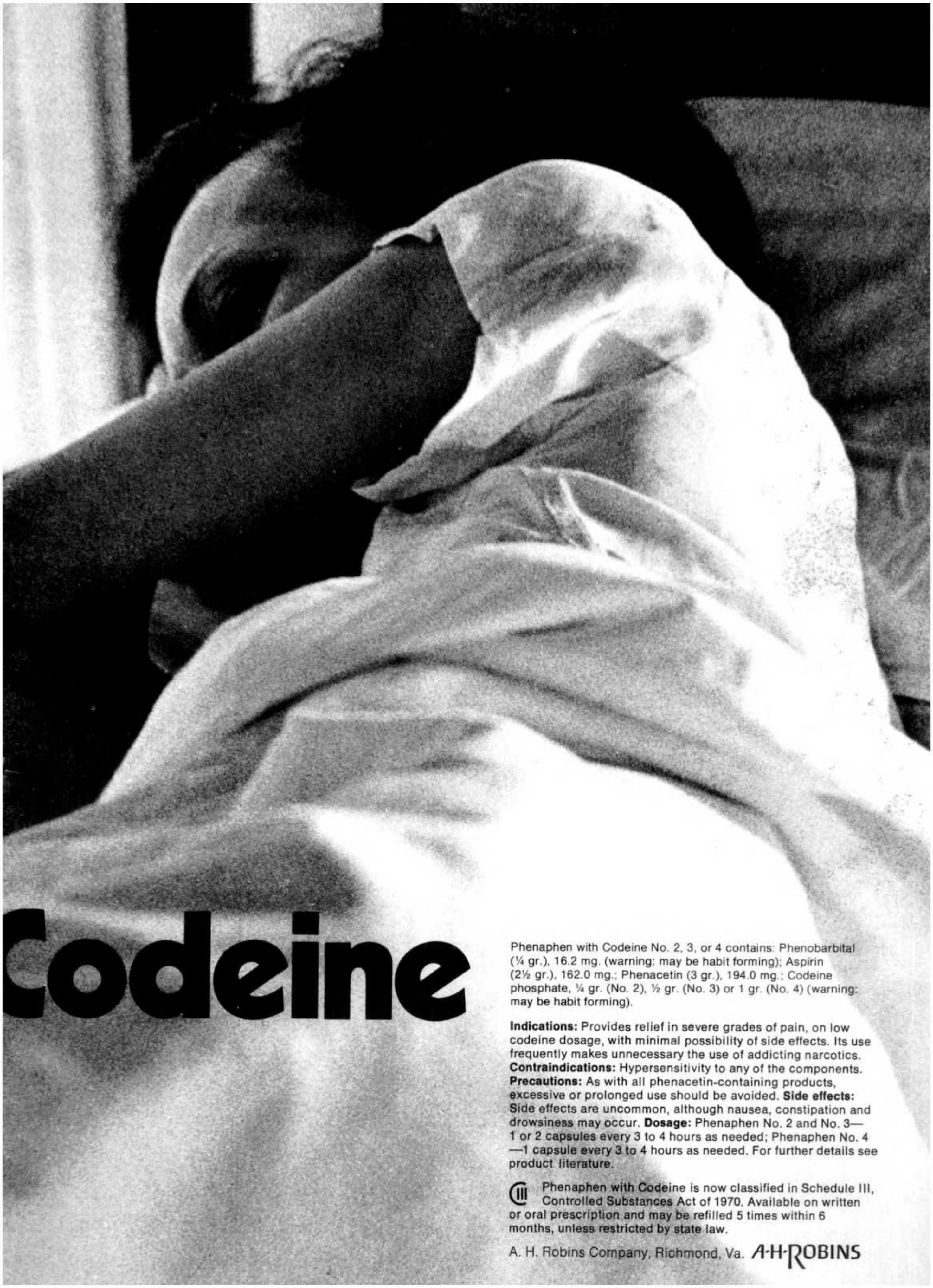
when pain goes on...
and on...
and on–

he analgesic formula that calms instead of caffeinates

Phenaphen® wit

or the patient with a terminal illness, PAIN past, present, and future can dominate is thoughts until it becomes almost an obsession. The more he is aware of the pain e is now experiencing, the more difficult it is to erase his memory of yesterday's ain, and to allay his fearful anticipation of tomorrow's pain.

urely the last thing this patient needs is an analgesic containing caffeine to stimulate he senses and heighten pain awareness. A far more logical choice is Phenaphen ith Codeine. The sensible formula provides ¼ grain of phenobarbital to take he nervous "edge" off, so the rest of the formula can help control the pain more ffectively. Don't you agree, Doctor, that psychic distress is an important factor most of your terminal and long-term convalescent patients?



Phenaphen with Codeine No. 2, 3, or 4 contains: Phenobarbital (¼ gr.), 16.2 mg. (warning: may be habit forming); Aspirin (2½ gr.), 162.0 mg.; Phenacetin (3 gr.), 194.0 mg.; Codeine phosphate, ¼ gr. (No. 2), ½ gr. (No. 3) or 1 gr. (No. 4) (warning: may be habit forming).

Indications: Provides relief in severe grades of pain, on low codeine dosage, with minimal possibility of side effects. Its use frequently makes unnecessary the use of addicting narcotics. **Contraindications:** Hypersensitivity to any of the components. **Precautions:** As with all phenacetin-containing products, excessive or prolonged use should be avoided. **Side effects:** Side effects are uncommon, although nausea, constipation and drowsiness may occur. **Dosage:** Phenaphen No. 2 and No. 3—1 or 2 capsules every 3 to 4 hours as needed; Phenaphen No. 4—1 capsule every 3 to 4 hours as needed. For further details see product literature.

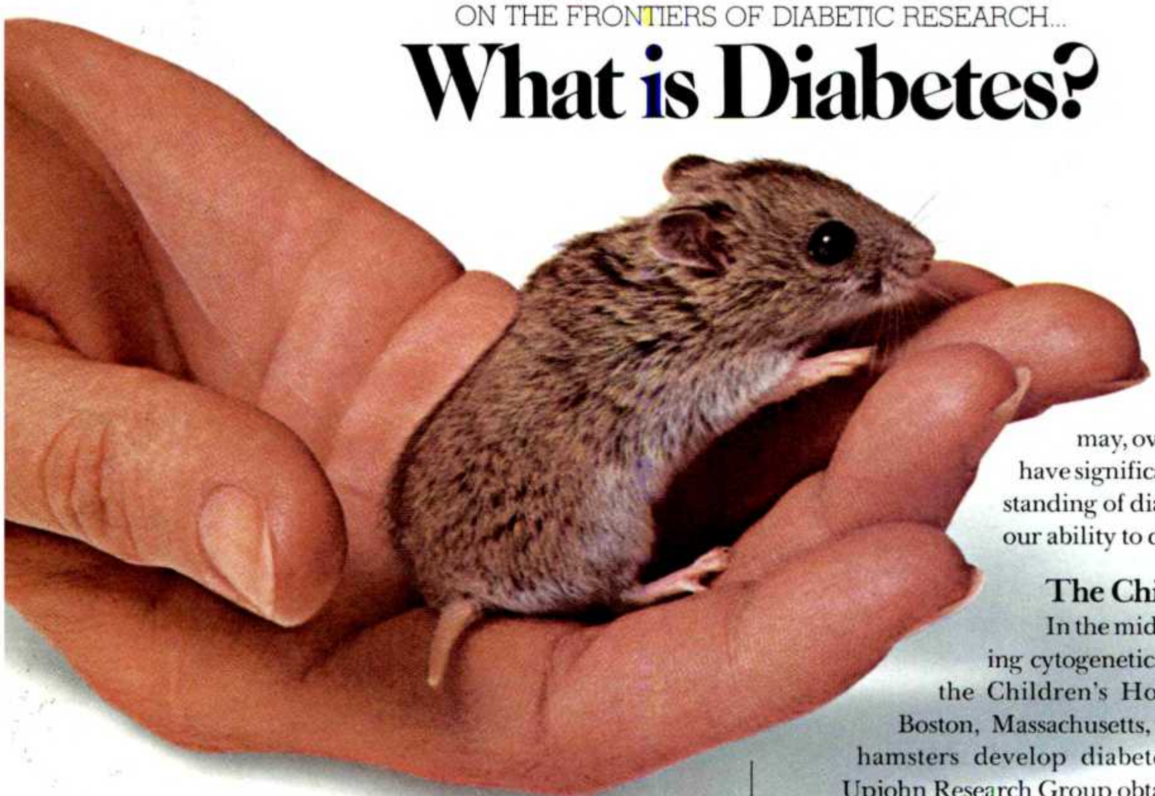
CIII Phenaphen with Codeine is now classified in Schedule III, Controlled Substances Act of 1970. Available on written or oral prescription and may be refilled 5 times within 6 months, unless restricted by state law.

A. H. Robins Company, Richmond, Va. A·H·ROBINS

Upjohn

ON THE FRONTIERS OF DIABETIC RESEARCH...

What is Diabetes?



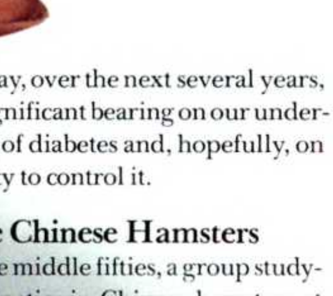
Although a medical scribe of ancient Egypt first made reference to diabetes mellitus in man, today, nearly 4000 years later, only meager specific knowledge exists as to the basic cause of the disease. Without such knowledge it has been possible to provide for limited control only *after* diabetes manifests itself in the form of elevated blood glucose. The possibility of prevention or even cure of diabetes, however, must depend on a full understanding of the genetic defect and/or defects underlying the disease. Our current understanding of diabetes may be compared to our former understanding of another disease of metabolic abnormality, phenylketonuria; only when the genetic lesion of that disease was discovered did it become possible to institute current programs of treatment.

Basic Diabetes Research at Upjohn

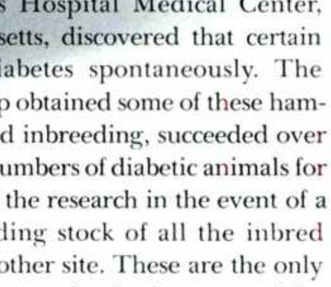
For more than ten years the Diabetes and Atherosclerosis Research Group at The Upjohn Company (W. E. Dulin, Director; G. C. Gerritsen; M. G. Soret; A. Y. Chang) has addressed itself, in a series of unique experiments, to the very basic question: What is diabetes? As with all such fundamental research, practical results are slow in coming and the work of the Group has at times raised more questions than it has been able to answer. It appears now, however, that the research is moving toward important conclusions which may, over the next several years, have significant bearing on our understanding of diabetes and, hopefully, on our ability to control it.

The Chinese Hamsters

In the middle fifties, a group studying cytogenetics in Chinese hamsters at the Children's Hospital Medical Center, Boston, Massachusetts, discovered that certain hamsters develop diabetes spontaneously. The Upjohn Research Group obtained some of these hamsters in 1962, and by controlled inbreeding, succeeded over the years in producing large numbers of diabetic animals for study. To assure continuity of the research in the event of a catastrophe, duplicate breeding stock of all the inbred families are maintained at another site. These are the only such colonies in the United States today. In the course of the research, Upjohn has cooperated with scientists in academic



Normal Chinese hamster, pancreatic tissue. Note blue-stained insulin granules which appear within the beta cells of the islet of Langerhans.



Diabetic Chinese hamster, pancreatic tissue. Insulin granules are almost totally absent. Though beta cells are present, there is some degranulization and vacuolization. The diabetic process is similar to that observed in human pancreatic tissue.

centers, both in America and abroad, in various specialized studies. When possible, these scientists have come to work for a time in Upjohn laboratories. In other cases, specially selected hamsters were transported to outside research facilities.

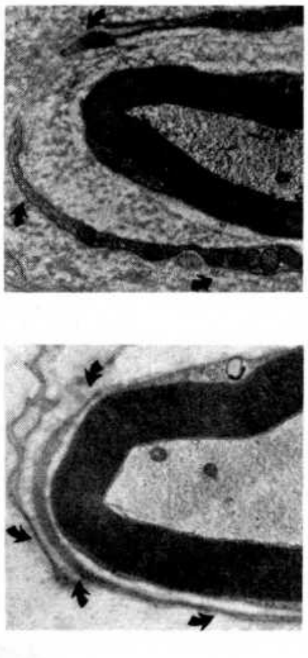
Closer to Man

While other species besides man develop diabetes spontaneously, the Chinese hamster appears to be the best laboratory animal model to study, since its disease is remarkably similar to diabetes in man. Chinese hamster diabetes, like human diabetes, is a complex disease. Like humans, the hamsters have more than one variety of diabetes, including the juvenile, insulin-dependent type as well as the maturity-onset type. They also develop pathological lesions in the retina, kidney, and peripheral nerves, as do human diabetics.

Diabetes is as complicated genetically in hamsters as it is in man. The type and severity of the disease appears to vary with the number of genes involved. Fortunately, genetic analysis can progress faster in the hamster since two or three generations can be produced per year.

Hamsters with Diabetic Genes Overeat

Perhaps one of the most significant observations is that hamsters with diabetic genes have significantly increased food consumption prior to development of clinical signs of diabetes. Further, if the animal with diabetic genes were limited to a normal amount of food, onset of diabetes could be delayed and reduced in severity, and the animal could have a normal life span of 34-35 months. Those animals that develop the clinical symptoms have a shorter life span, which varies with the severity of the disease. Interestingly, decreases in the incidence of human diabetes were noted during the siege of Paris in 1870, and during and immediately after World War II in Europe. It has been postulated that decreased food intake during these periods may have delayed the onset of the disease or reduced its severity to a point where hyperglycemia did not appear.



Peripheral diabetic neuropathy. Top photo, Chinese hamster; bottom photo, 58-year-old diabetic man. The encirclement of myelinated nerve fibers by thin Schwann cell processes, indicated by arrows, is a cellular reaction to chronic demyelination, and is a characteristic finding in this condition in both man and the Chinese hamster.

Implications for the Future

The purpose of the Upjohn Research Group is to attempt, through its work with the Chinese hamsters, to find the basic genetic lesion or lesions associated with diabetes. Such knowledge could provide the information necessary to predict the disease in humans, to define its exact mode of inheritance, and to initiate studies aimed at correcting the defect or defects. Hopefully, it will eventually be possible to devise methods to prevent the development of the abnormalities associated with the disease, if the defect or defects can be corrected. Such methods may replace all treatment in use today.

Already, a beginning has been made in the establishment of programs to apply the information gained from the hamster research. The Upjohn Group is currently working with pediatric endocrinologists in an attempt to define the genetics of human diabetes and to confirm retrospectively whether the discoveries concerning dietary manipulation in genetically diabetic hamsters can be applied to humans. Should the results of these investigations be positive, and if it becomes possible through further work with the hamsters to identify prediabetic humans before they develop signs of the disease, an enormous stride will have been made. Even though the investment in this research is made with no guarantee, this risk must be undertaken.

Note: For bibliography of published papers, please write to W. E. Dulin, PhD, Upjohn Diabetes and Atherosclerosis Research Group, 7241-25-9, Kalamazoo, Michigan 49001.

DEDICATED TO HEALTH CARE

Meeting mankind's health needs is a
primary commitment of The Upjohn
Company. This commitment is fulfilled
not only through the production of
today's pharmaceuticals, but even more
importantly, through a continuing
dedication to research and development
of programs directed at discovery of the
therapy and therapeutic approaches of
the future.

Upjohn

The Upjohn Company
Kalamazoo, Michigan 49001

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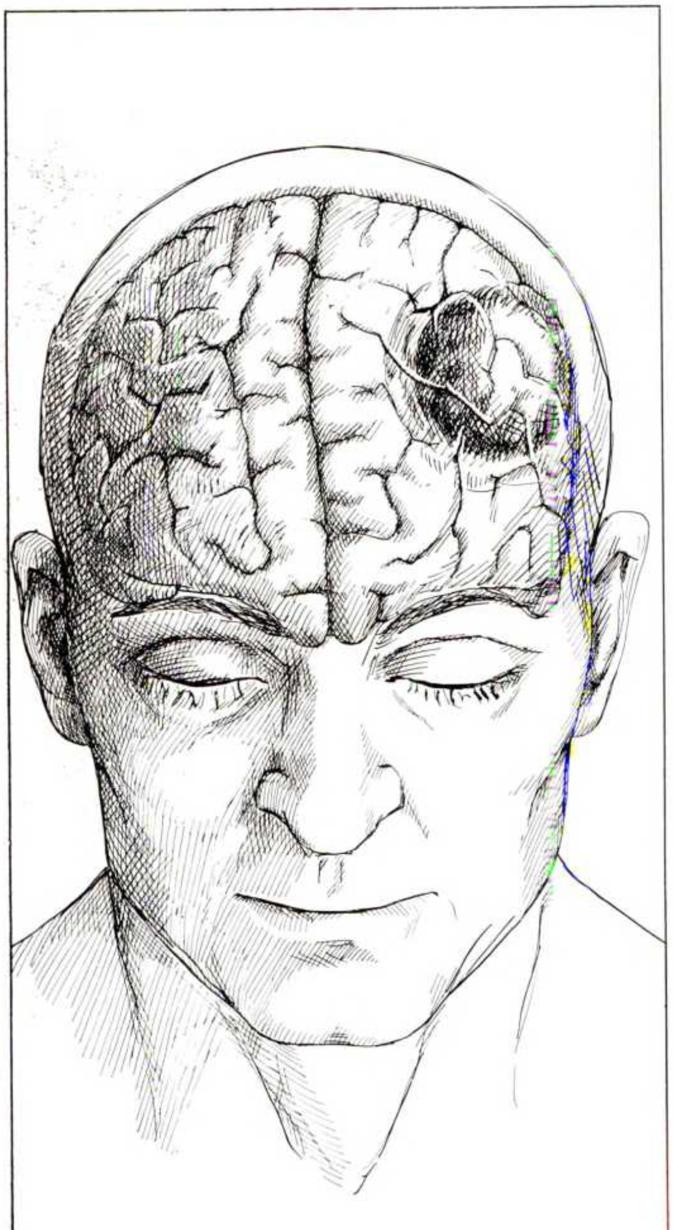
cerebral

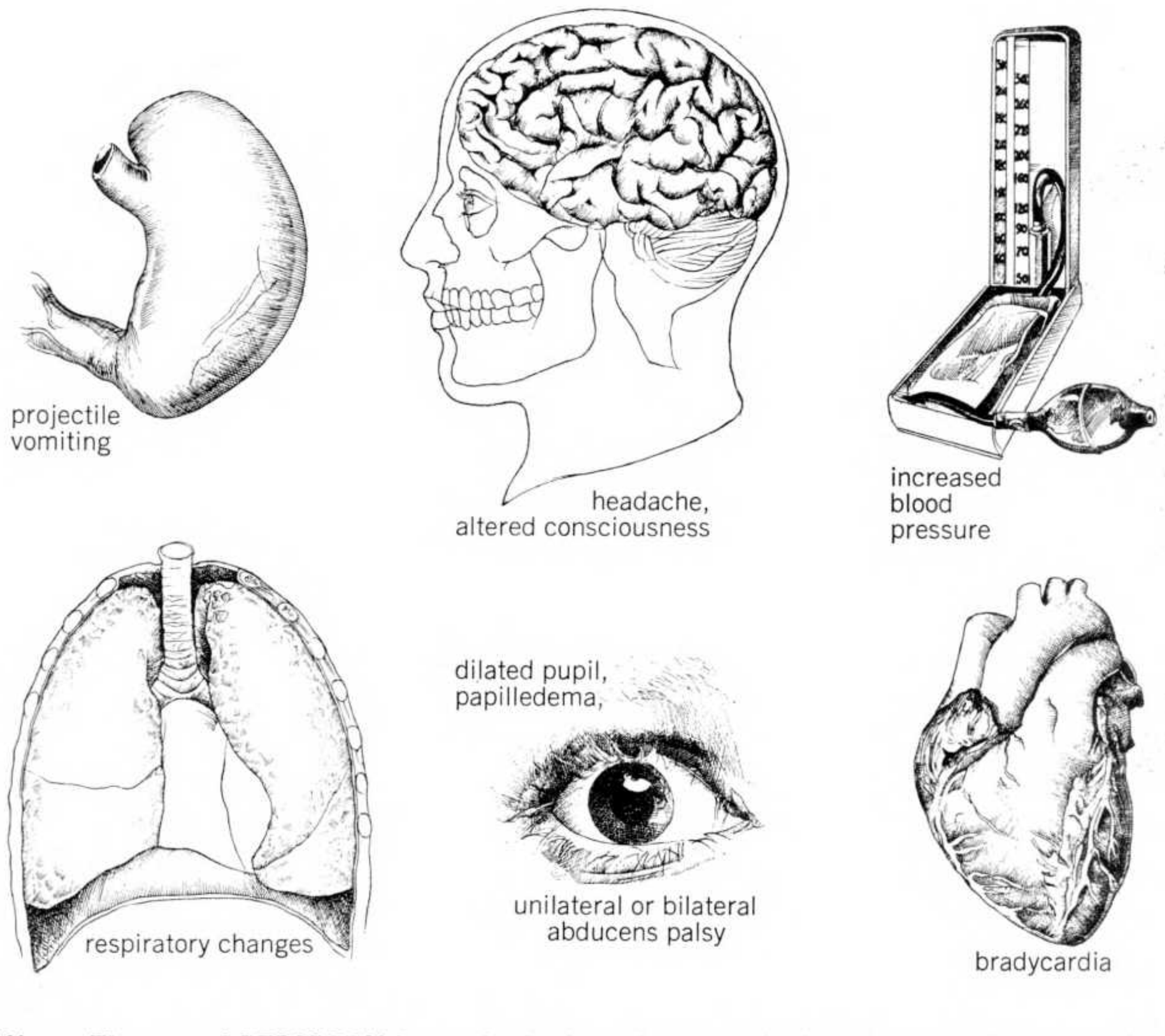
expect it as a possible complication of primary or metastatic brain tumor.



expect it in the presence of severe head injury.

edema*

suspect it in the presence of signs and symptoms such as these:



***Note: The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.**

Injection: 4 mg/ml Phosphate

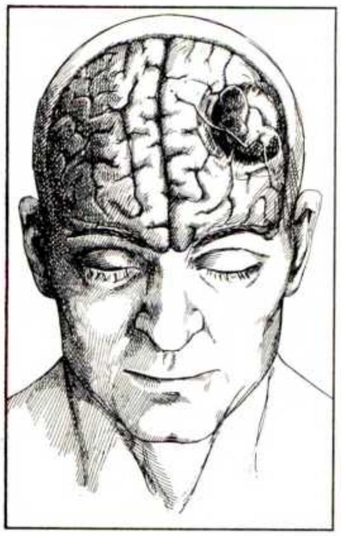
an indication for **DECADRON**® (Dexamethasone Sodium Phosphate|MSD)

and

Tablets: 1.5 mg, 0.75 mg, 0.5 mg, 0.25 mg

DECADRON® (Dexamethasone|MSD)

For a brief summary of prescribing information, please see following page.



Injection Decadron Phosphate®

(Dexamethasone Sodium Phosphate|MSD)

"Some degree of edema accompanies most head injuries. Various methods have been used to control this, but at present the most efficient method is use of . . . dexamethasone [DECADRON®]. . . . The effect of this is not well understood, but there is little question that edema of the brain is significantly lessened by its use."

Ritchie WP: The emergency care of cerebral injuries, J Lancet *86*:255, June 1966.

The use of DECADRON in cerebral edema is not a substitute for careful neurosurgical evaluation and definitive management such as neurosurgery or other specific therapy.

Dosage for cerebral edema

Injection DECADRON Phosphate is generally administered initially in a dosage of 10 mg dexamethasone phosphate (2.5 ml) IV followed by 4 mg dexamethasone phosphate (1 ml) IM every six hours until symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For the palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy should be individualized with either Injection DECADRON Phosphate or Tablets DECADRON (supplied as 1.5-, 0.75-, 0.5-, and 0.25-mg tablets). Two mg two or three times daily may be effective. The smallest dosage necessary to control cerebral edema should be utilized. The usual precautions in regard to corticosteroid therapy should be employed, and antacids, anticholinergic drugs, and diet measures to prevent gastrointestinal ulcer or hemorrhage should be considered. Please read the brief summary below, and consult full prescribing information before prescribing or administering.

Contraindications: Systemic fungal infections.

Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

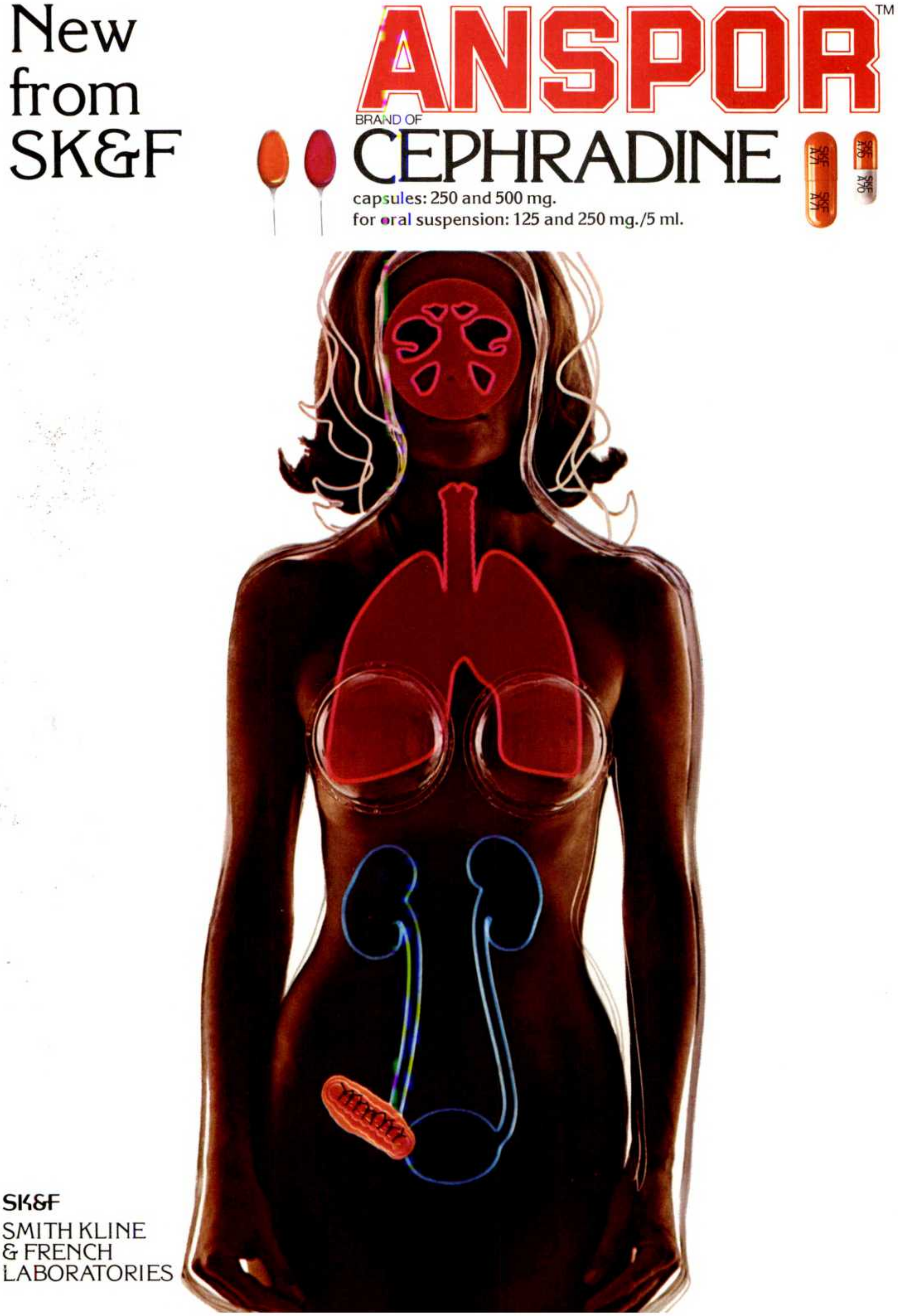
How Supplied: Tablets in four strengths: 1.5 mg dexamethasone, in bottles of 50; 0.75 mg dexamethasone, in 5-12 PAK® (package of 12), single-unit packages of 100, and bottles of 100 and 1000; 0.5 mg dexamethasone, in bottles of 100 and 1000; and 0.25 mg, in bottles of 100. Injection, in 1-ml disposable syringes and 1-ml, 5-ml, and 25-ml vials, containing per ml: dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone, 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, water for injection q.s. 1 ml, and 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.

For more detailed information, consult your MSD representative or see full prescribing information. Merck Sharp & Dohme, Division of Merck & Co., INC., West Point, Pa. 19486

Tablets
DECADRON®
(Dexamethasone|MSD)

Injection Phosphate
DECADRON®
(Dexamethasone Sodium
Phosphate|MSD)

MSD
MERCK
SHARP&
DOHME



New
from
SK&F

ANSPOR™

BRAND OF
CEPHRADINE

capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.

SK&F
SMITH KLINE
& FRENCH
LABORATORIES

A New Oral Antibiotic with these Important Features:

- **Bactericidal activity *in vitro.***
- **Effective against a wide range of Gram-positive and Gram-negative infections due to susceptible organisms:**

Respiratory tract infections caused by group A beta-hemolytic streptococci and *D. pneumoniae.*

Urinary tract infections caused by *E. coli, Pr. mirabilis,* and *Klebsiella* species.

Skin and soft-tissue infections caused by staphylococci.

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae, H. influenzae* and staphylococci.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

- **Documented safety.**
- **Rapidly absorbed. Average peak serum levels within 1 hour.**

(Approximately 9 and 16.5 mcg./ml. at 1 hour with 250 and 500 mg. capsules, respectively, in normal adult volunteers.)

- **High urinary levels.**

(Peak concentration of approximately 3200 mcg./ml. with 500 mg. capsule dose in normal adult volunteers.)

- **Excreted essentially unchanged in the urine.**
- **Acid stable. Can be given without regard to meals.**

'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. **In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.**

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

New from SK&F

ANSPOR™

BRAND OF
CEPHRADINE

capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephradine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella sp.
Hemophilus influenzae

Note—Some strains of enterococci *(Streptococcus faecalis)* are resistant to cephradine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated microorganisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*. *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Anspor (cephradine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal function. In known or suspected renal impairment, careful clinical observation and appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See *DOSAGE AND ADMINISTRATION* section for information on treatment of patients with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the urine may occur with Benedict's solution, Fehling's solution, or with Clinitest* tablets, but not with enzyme-based tests such as Clinistix* and Tes-Tape.*

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pruritus, and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompanied by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the chest and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephradine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally spaced doses. For acute infections of the urinary tract, including prostatitis, and pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equally divided and spaced doses. For otitis media due to *H. influenzae*, doses from 75 to 100 mg./kg./day in equally divided and spaced doses are recommended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram, q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule is necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance dose is 500 mg. at following time intervals: creatinine clearance >20 ml./min., 6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-24 hours between doses; creatinine clearance 10-14 ml./min., 24-40 hours between doses; creatinine clearance 5-9 ml./min., 40-50 hours between doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

HOW SUPPLIED

ANSPOR (cephradine, SK&F) Capsules—250 and 500 mg.

'ANSPOR' for Oral Suspension—Pleasant fruit-flavored oral suspension which, after reconstitution, provides 125 mg. or 250 mg. of cephradine per 5 ml. teaspoonful.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa. 19101

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contains aspirin

Darvon® Compound-65
propoxyphene hydrochloride, aspirin,
phenacetin, and caffeine

Actions: Propoxyphene hydrochloride is a mild analgesic structurally related to the narcotic analgesic methadone; though propoxyphene's general pharmacologic properties are those of the narcotics as a group, it does not compare with them in analgesic potency.

The combination of propoxyphene with a mixture of aspirin, phenacetin, and caffeine (APC compound) produces greater analgesia than that produced by either propoxyphene or APC compound administered alone.

Indication: For the relief of mild to moderate pain.

Contraindication: Hypersensitivity to propoxyphene, aspirin, phenacetin, or caffeine.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Salicylates should be used with extreme caution in the presence of peptic ulcer or coagulation abnormalities.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine.

The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Phenacetin has been reported to damage the kidneys when taken in large amounts for a long time.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychoses and convulsions.

Administration and Dosage: A narcotic prescription is not required.

Darvon Compound-65 is given orally. The usual dosage is 1 Pulvule® every four hours as needed for pain. Each Pulvule contains 65 mg. propoxyphene hydrochloride, 227 mg. aspirin, 162 mg. phenacetin, and 32.4 mg. caffeine.

How Supplied: Pulvules Darvon® Compound-65 (propoxyphene hydrochloride, aspirin, phenacetin, and caffeine, Lilly), in bottles of 500, in Identi-Dose® (unit dose medication, Lilly) in boxes of 100, and in Rx Paks (prescription packages, Lilly) in bottles of 100, in 25 packages of 30, and in 20 packages of 50.

[050374]

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Darvocet-N® 100

100 mg. propoxyphene napsylate and 650 mg. acetaminophen

contains no aspirin

Darvocet-N®
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Description: Each tablet of Darvocet-N contains 50 mg. propoxyphene napsylate and 325 mg. acetaminophen.

Each tablet of Darvocet-N 100 contains 100 mg. propoxyphene napsylate and 650 mg. acetaminophen.

Indication: These products are indicated for the relief of mild to moderate pain, either when pain is present alone or when it is accompanied by fever.

Contraindications: Hypersensitivity to propoxyphene or to acetaminophen.

Warnings: *Drug Dependence*—Propoxyphene can produce drug dependence characterized by psychic dependence and, less frequently, physical dependence and tolerance. Propoxyphene will only partially suppress the withdrawal syndrome in individuals physically dependent on morphine or other narcotics. The abuse liability of propoxyphene is qualitatively similar to that of codeine although quantitatively less, and propoxyphene should be prescribed with the same degree of caution appropriate to the use of codeine.

Usage in Ambulatory Patients—Propoxyphene may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Usage in Pregnancy—Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, propoxyphene should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children—Propoxyphene is not recommended for use in children, because documented clinical experience has been insufficient to establish safety and a suitable dosage regimen in the pediatric age group.

Precautions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

Adverse Reactions: The most frequent adverse reactions are dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include constipation, abdominal pain, skin rashes, lightheadedness, headache, weakness, euphoria, dysphoria, and minor visual disturbances.

The chronic ingestion of propoxyphene in doses exceeding 800 mg. per day has caused toxic psychosis and convulsions.

Administration and Dosage: A narcotic prescription is not required.

These products are given orally. The usual dose is 100 mg. propoxyphene napsylate and 650 mg. acetaminophen every four hours as needed for pain.

Drug Interactions: Confusion, anxiety, and tremors have been reported in a few patients receiving propoxyphene concomitantly with orphenadrine. The central-nervous-system depressant effect of propoxyphene may be additive with that of other C.N.S. depressants.

How Supplied: Tablets Darvocet-N® and Darvocet-N® 100 (propoxyphene napsylate with acetaminophen, Lilly), in an Rx Pak (prescription package, Lilly) in 20 packages of 50, in bottles of 100 (Rx Pak) and 500, and in Identi-Dose® (unit dose medication, Lilly) in boxes of 100. Darvocet-N 100 is also available in an Rx Pak in 25 packages of 30. [102373]

Additional information available to the profession on request.

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The Response to Methosarb®
(calusterone, Upjohn)

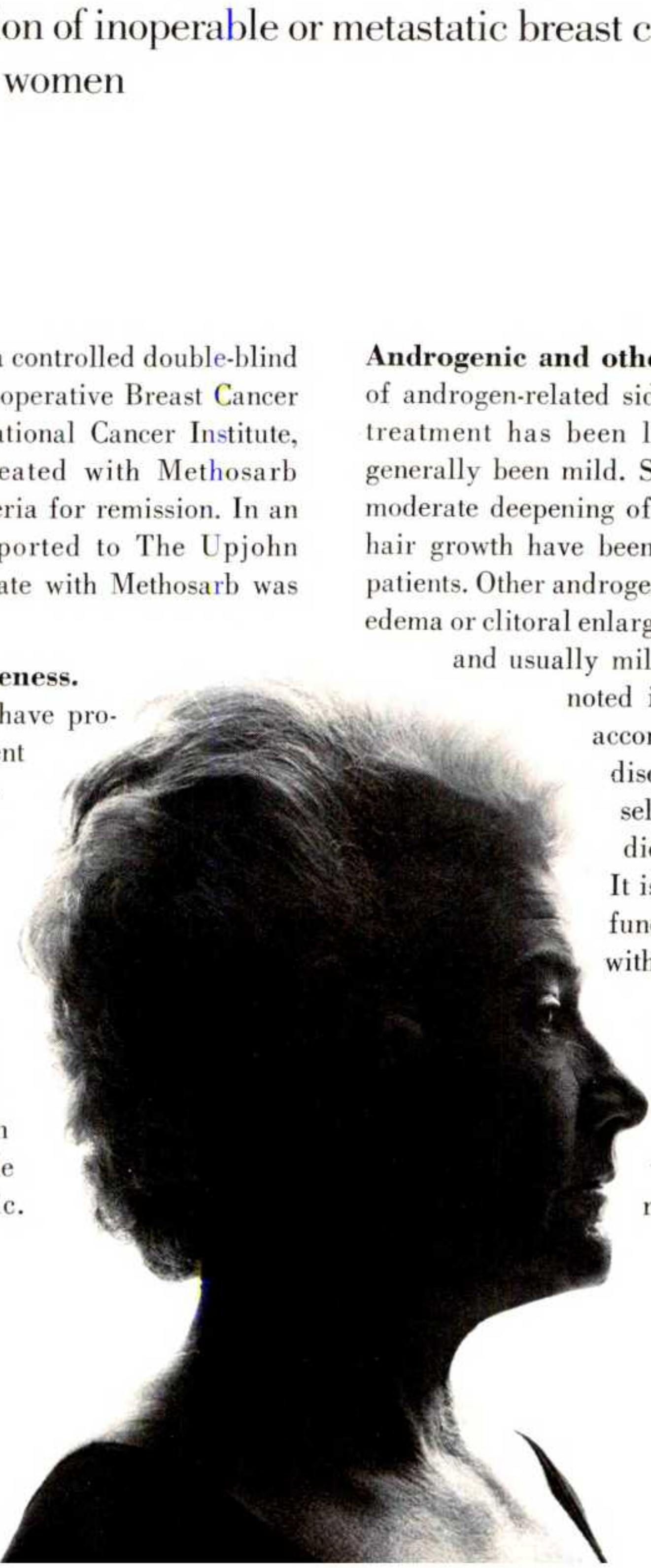
an agent for palliation of inoperable or metastatic breast cancer in postmenopausal women

Rate of remission. In a controlled double-blind study conducted by the Cooperative Breast Cancer Group (CBCG) of the National Cancer Institute, 28% of 109 patients treated with Methosarb (calusterone) met the criteria for remission. In an additional 750 cases reported to The Upjohn Company, the remission rate with Methosarb was approximately 21%.

The measure of effectiveness. Methosarb was judged to have produced remission if treatment resulted in one of three responses: (1) a measurable decrease in the size of *all* demonstrable tumor masses; (2) a decrease in the size of more than 50% of nonosseous lesions, with all bone lesions remaining static; or (3) improvement of more than 50% of total lesions while the remainder were static.

Androgenic and other effects. The incidence of androgen-related side effects during Methosarb treatment has been low, and the effects have generally been mild. Side effects such as mild or moderate deepening of the voice, acne, and facial hair growth have been seen in about 20-25% of patients. Other androgen-related side effects such as edema or clitoral enlargement have been uncommon and usually mild. Hypercalcemia has been noted in a few cases, but usually accompanied progression of the disease. Change in libido was seldom seen. Cholestatic jaundice has rarely been reported. It is advisable to perform liver function tests during treatment with Methosarb.

Androgens are contraindicated in carcinoma of the male breast and in premenopausal women in whom ovarian function has not been terminated.



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Methosarb® tablets, 50 mg
(calusterone)

Description: Methosarb (calusterone) is a synthetic steroid related to testosterone, and is chemically designated 7β, 17α-dimethyl-17β-hydroxyandrost-4-en-3-one, or 7β, 17-dimethyltestosterone.

Action: The biochemical mechanism by which Methosarb (calusterone) produces its clinical effects in the treatment of breast cancer is at present unknown.

Methosarb has been found to be effective in about 25% of patients with advanced or disseminated mammary cancer evaluated according to the following criteria: (1) a measurable decrease in size of *all* demonstrable tumor masses; (2) a decrease in the size of more than 50% of non-osseous lesions, with all bone lesions remaining static; or (3) an improvement of more than 50% of total lesions while the remainder were static.

Indications: Methosarb (calusterone) is recommended only for the palliative therapy of advanced inoperable or metastatic carcinoma of the breast in postmenopausal women when hormonal therapy is indicated. It may also be used in women who were diagnosed as having had disseminated breast carcinoma when premenopausal and in whom ovarian function has been subsequently terminated.

Contraindications: Androgens are contraindicated in carcinoma of the male breast and in premenopausal women.

Warnings: *Usage in Pregnancy.* Since safe use of Methosarb (calusterone) has not been established with respect to adverse effects upon fetal development, and since this preparation is intended for use only in postmenopausal women, Methosarb should not be used during pregnancy. Methosarb in teratology studies performed in rabbits and rats is suggestive of producing litters exhibiting signs of immaturity at birth as compared to control litters.

Precautions: In general, the usual precautions pertaining to the use of androgens should apply to Methosarb (calusterone), although the androgenic effects noted with Methosarb are of low incidence and are generally mild. Plasma calcium levels should be routinely determined in any patient receiving therapy for mammary cancer since hypercalcemia may occur at times, particularly during periods of active remission of bony metastases. If hypercalcemia occurs, appropriate measures should be instituted. Drug-related edema may occasionally be seen and is usually mild. Patients with significant edema may require diuretics before and during treatment with this steroid.

Objective evidence of tumor progression should be evaluated periodically by physical examination, x-rays of known or suspected metastases, and determinations of serum calcium and alkaline phosphatase levels. The latter determination may reflect improvement in osseous lesions if there is a slight to moderate rise after initiation of treatment, or it may be indicative of extensive hepatic metastases if the level is markedly elevated.

Methosarb may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may require reduction in order to maintain a satisfactory therapeutic hypoprothrombinemia.

Mild increases in Bromsulphalein (BSP) retention have been noted in a few patients, and increases in serum glutamic oxaloacetic transaminase (SGOT) to abnormal levels were seen in about 20% of the patients. Many of these patients had progressive disease with liver involvement. Few showed the concomitant increases in serum bilirubin and alkaline phosphatase that might suggest drug-related excretory dysfunction. Cholestatic jaundice has rarely been reported. It is therefore advisable to perform liver function tests during treatment with Methosarb.

There are no reports of the use of this agent in carcinoma of the breast during pregnancy or in carcinoma of the breast in males with or without associated carcinoma of the prostate.

Adverse Reactions: Androgen-related side effects such as mild or moderate deepening of the voice, acne, and facial hair growth are seen in about 20-25% of the patients. Other androgen-related side effects, such as edema or clitoral enlargement, are uncommon and are usually mild. Hypercalcemia was noted in a few cases but usually accompanied progression of the disease. Libido seldom seems to be affected.

Increases in nausea and vomiting, seen in about 5-10% of patients, were usually mild or moderate and controllable, but a few cases of severe vomiting required discontinuation of therapy. Brief periods of intensely increased pain have been reported in a few patients experiencing osseous flares. The few other signs and symptoms that have been reported in association with the use of this drug have been related to the underlying disease state.

Dosage and Administration: The usual oral dose is 200 mg per day, administered as 50 mg tablets, q.i.d., although doses of 150-300 mg/day have been successfully used.

In order to evaluate the response, therapy with Methosarb (calusterone) should be continued for a minimum of three months, unless there is active progression of the disease.

Therapy with Methosarb should not replace supportive measures such as transfusion, antibacterial therapy, or the use of corticosteroids.

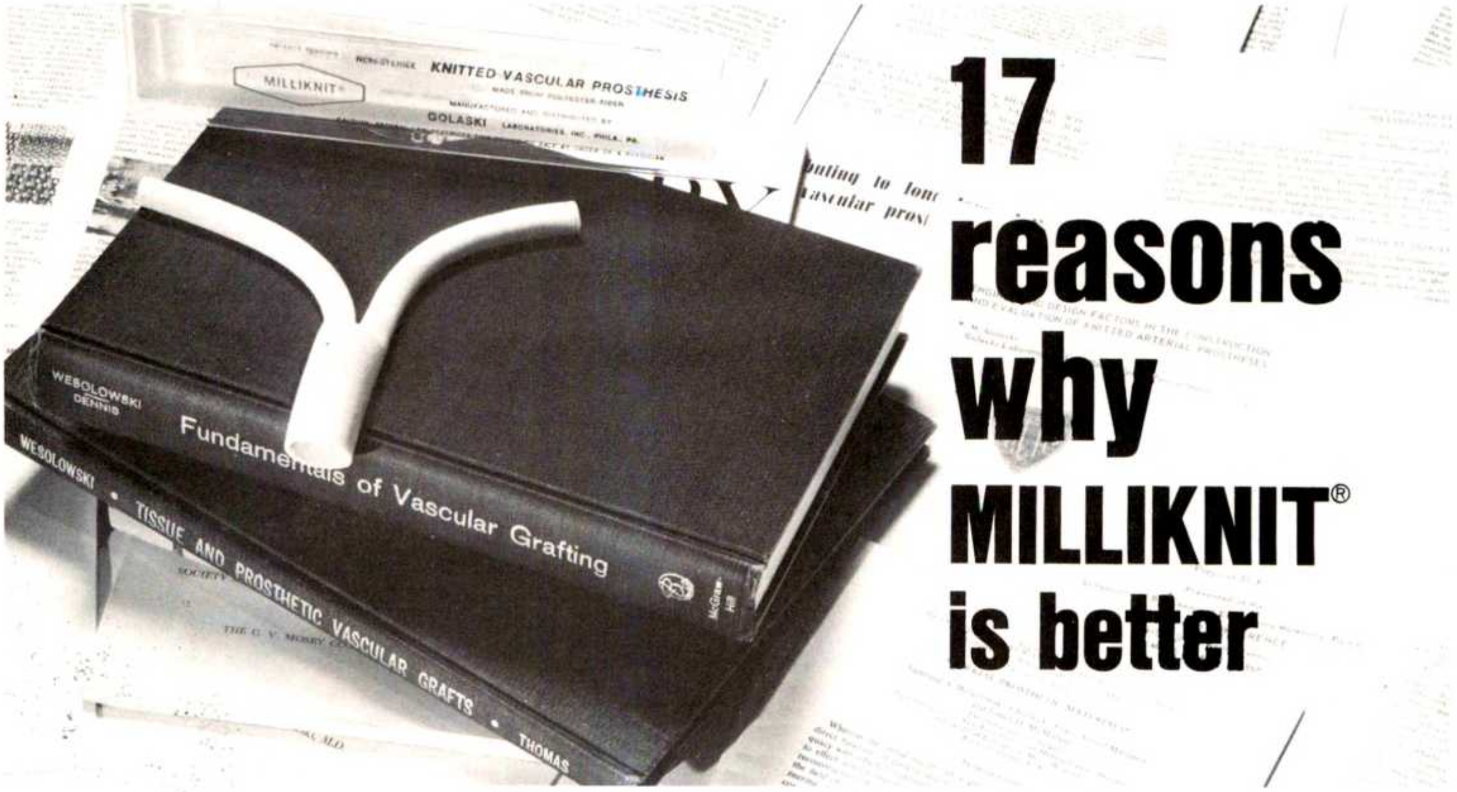
How Supplied: Methosarb (calusterone) is available as tablets containing 50 mg of calusterone, in bottles of 120.

Caution: Federal law prohibits dispensing without prescription. NDC J-4027-4

Methosarb® 50mg tablets (calusterone, Upjohn)

for the palliation of inoperable or metastatic breast cancer in postmenopausal women

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001, U.S.A.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Roux-en-Y Hepaticojejunostomy:

A Reappraisal of its Indications and Results

PARIDE STEFANINI, M.D., MANLIO CARBONI, M.D., NERI PATRASSI, M.D., ANTONIO BASOLI, M.D.,
GIANCARLO DE BERNARDINIS, M.D., PAOLO NEGRO, M.D.

*From the Second Surgical Clinic,
Third Surgical Pathology of the
University of Rome and Surgical
Pathology of the University of L'Aquila,
Italy*

A critical evaluation is made of 131 patients submitted to choledocho or hepaticojejunostomy. The main indications for hepaticojejunostomy were iatrogenic strictures of CBD (60 patients), and choledocholithiasis with markedly dilated duct (41 patients). The overall mortality rate was 4% representing principally renal hepatic failure, bile peritonitis and bleeding. The complications following hepaticojejunostomy included only in one case biliary fistula which required reoperation. The long-term results of 80 patients available for a followup study were as follows: 63 patients (78.7%) were symptom-free at 2–13 years followup; 8 patients had brief episodes of cholangitis which responded to antibiotic and corticosteroid treatment; 9 patients required reoperation for stricture of anastomosis. These overall results are a strong argument for hepaticojejunostomy which, compared with choledochoduodenostomy, avoids the hazards of the so-called sump syndrome and of the reflux of enteric contents in the CBD. An increased incidence of peptic ulcer disease in the patients submitted to hepaticojejunostomy was not observed. In very high strictures and in reinterventions anastomosis between left hepatic duct and Roux-en-Y jejunal limb was carried out. The results achieved with this technique, which was performed in 26 patients, were about the same following hepaticojejunostomy.

DESPITE voluminous literature on the treatment of choledocholithiasis and benign obstructions of common bile duct (CBD), there are few studies in which an attempt has been made to suggest the indications for each surgical procedure. Three operations have been commonly employed for the correction of these lesions, namely sphincteroplasty, choledochoduodenostomy and hepaticojejunostomy. It is generally agreed that sphincteroplasty is the procedure of choice in the treatment of lithiasis of distal CBD and stenosis at the sphincter of Oddi.[9,15,20,26] Conversely, choledochoduodenostomy is usually advised in patients with choledocholithiasis, iatrogenic stricture, inflammatory stenosis and chronic pancreatitis.[1,4,7,8,22] Moreover, there is a fairly uniform pattern in limiting the extent of indications of hepaticojejunostomy only to the strictures in the proximal CBD caused by surgical trauma.[3,17]

The purpose of the present paper is to advocate hepaticojejunostomy as opposed to choledochoduodenostomy in treating obstructions of proximal as well as distal CBD. In addition, hepaticojejunostomy is advised as the most appropriate procedure also in patients with choledocholithiasis and markedly dilated duct. Specific indications and contraindications for hepaticojejunostomy have been determined by the immediate and long-term results of 131 patients operated upon at the 2nd Surgical Clinic of the University of Rome during the years 1960–73.

Operative Technique

Of the total of 140 operations performed in 131 patients, there were 114 anastomoses between CBD and Roux-en-Y jejunal limb. In addition, 26 anastomoses between left hepatic duct and jejunum were performed according to the technique first described by Hepp and Couinaud[6] (Fig. 1), six of which were carried out for recurrence of CBD stricture following hepaticojejunostomy. The choice of the Hepp procedure, employed when sufficient CBD tissue was not present, was supported by the rationale that the first portion of left hepatic duct parallels the hilum of the liver and is easier to dissect than right hepatic duct which directly goes into the hepatic parenchyma. Moreover this portion of left hepatic duct does not cross any blood vessel and does not receive any biliary duct. The anastomosis between left

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Submitted for publication April 26, 1974.

Address correspondence to: Paride Stefanini, M.D., 2nd Surgical Clinic, University of Rome Medical School, Policlinico Umberto I, 00161, Rome, Italy.

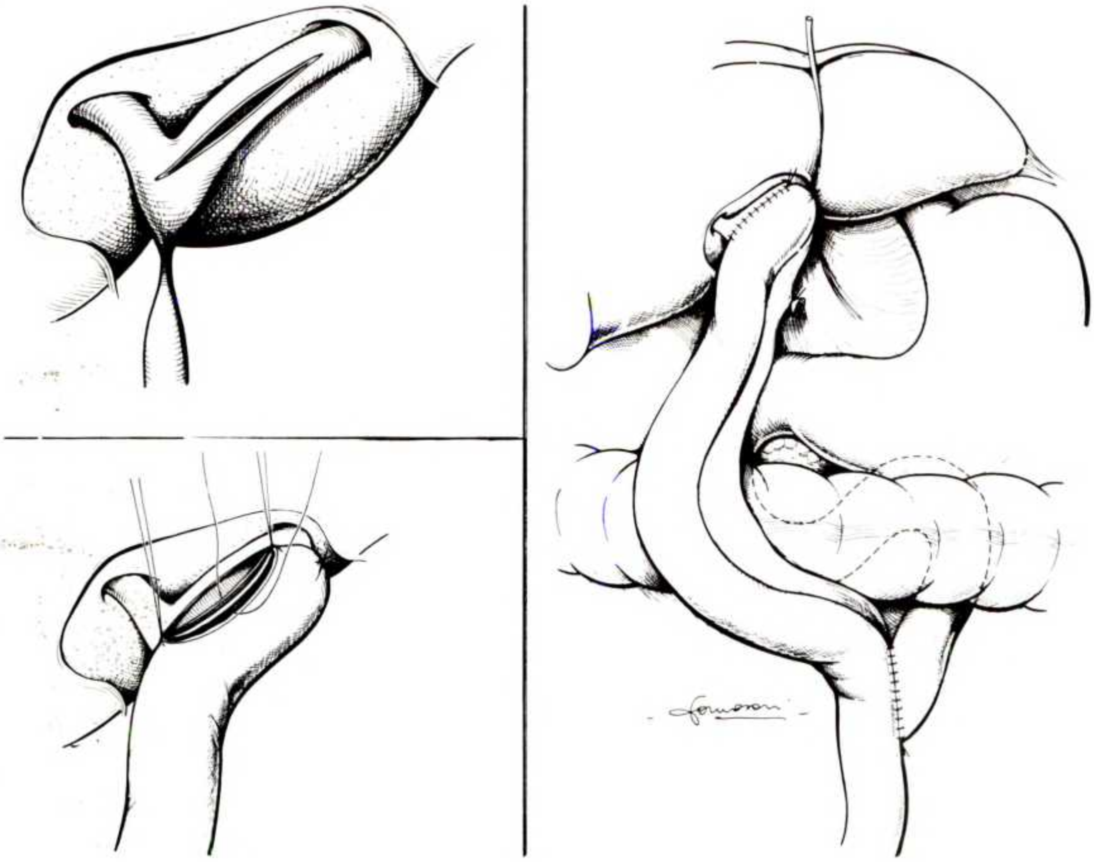

FIG. 1. Technique for anastomosis between left hepatic duct and Roux-en-Y jejunal limb, according to Hepp and Couinaud.

hepatic duct and the jejunal limb was fashoned in a side-to-side manner, while the hepatico or choledochojejunostomy was performed in an end-to-side manner. The Roux-en-Y jejunal limb was transected at 30–35 cm from the ligament of Treitz, where the mesentery is of sufficient length to permit its being delivered into the hilar region of the liver, and was placed in antecolic position. The anastomosis of both procedures was made using interrupted 3-0 chronic catgut sutures in the inner layer, and 3-0 silk sutures in serosal layer. In recent years, a single layer of interrupted 3-0 silk sutures with atraumatic needles was preferred. A fenestrated straight catheter across the anastomosis and brought out through the jejunal limb was routinely used. In the patients with choledocholithiasis it was employed only to drain and to splint the anastomosis and was removed in two or three weeks. Conversely, in patients with iatrogenic stricture the tube was placed as a stent to allow fibrous tissue to mature without narrowing. In these cases the stent was left in place for 40–60 days (Fig. 2). Only two patients had a transhepatic tube placed as described by Smith.[19]

Clinical Material

Of the 131 patients who underwent hepaticojejunostomy, 51 were male and 80 were female. The age range was 31–73 years, with an average of 56 years.

Indications for hepaticojejunostomy in 131 patients operated upon are summarized in Table 1. In 74 patients the bile duct stricture was due to operative injury incurred during the course of other surgical procedures. The extrahepatic biliary tree was damaged during cholecystectomy in 59 cases and during gastrectomy in five cases, while the stricture occurred after choledochoduodenostomy in six patients and after choledochotomy and Kehr-tube in four patients. Bile duct stricture and fistula by surgical injury

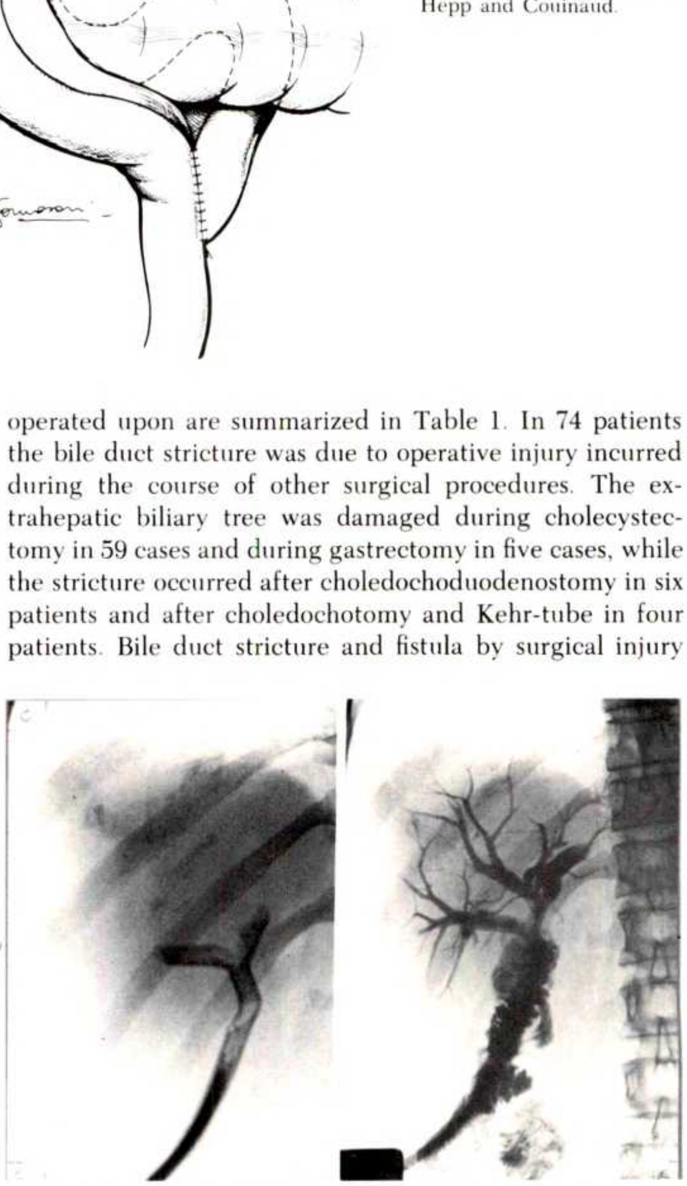

FIG. 2. Radiograms showing the use of transanastomotic drainage as a stent in a patient submitted to hepaticojejunostomy.

TABLE 1. *Indications for Hepaticojejunostomy in 131 Patients*

	No. of cases	%
Iatrogenic stricture	60	47
Choledocholithiasis (CBD diameter over 1.5 cm)	41	32
Iatrogenic stricture and fistula	14	11
Wide inflammatory stenosis	5	3
Chronic pancreatitis	5	3
Choledocholithiasis and fistula	3	2
Congenital choledochal cyst	3	2
Total	131	100

were found in 14 patients, three of which had a complete excision of biliary tree recognized at operation (Fig. 3). Indication for hepaticojejunostomy in 41 patients was choledocholithiasis with common duct markedly dilated (Fig. 4), in five patients chronic pancreatitis (Fig. 5) and in five patients wide inflammatory stenosis with choledocholithiasis (Fig. 6).

The surgical procedures performed before hepaticojejunostomy are shown in Table 2. Of 131 patients, 119 had previously one operation, 62 had two operations, 14 had three operations and 2 had four operations before they were admitted to the 2nd Surgical Clinic of the University of Rome. The average number of operations per patient in this series was 2.4, including the 140 hepaticojejunostomies. In 12 patients with cholelithiasis, choledocholithiasis and widely dilated common duct, hepaticojejunostomy was performed as the first procedure.

Mortality, Morbidity and Long-term Results

In 131 patients submitted to hepaticojejunostomy there were six postoperative deaths, one due to bile peritonitis, one due to cardiac failure and three due to renal hepatic failure. The sixth patient who had biliary cirrhosis died of bleeding from esophageal varices. Consequently, the overall mortality rate is about 4%. However, it was lowered to 3% in the last years with increasing experience in these techniques. Only one patient who had choledocholithiasis, biliary fistula and markedly dilated duct died following hepaticojejunostomy. The others had biliary duct stricture due to operative injury and were previously submitted to several attempt of surgical repair to achieve adequate biliary drainage. Two of these patients died following hepaticojejunostomy performed in our clinic.

The overall morbidity was 13.5% representing principally atelectasis or pneumonitis, subphrenic absess, hepatic renal failure and bleeding. Only in one case following hepaticojejunostomy biliary fistula developed that required reoperation.

Of 127 patients surviving to operation, 80 (61%) were available for a followup study. The long-term results of the patients submitted to hepaticojejunostomy are shown in Table 3. Sixty-three patients (78.7%) were symptom-free at 2–13 years followup and consequently have maintained a functioning anastomosis without development of recurrent stricture. All the patients in whom hepaticojejunostomy was performed as first procedure were followed for long periods and had no signs of cholangitis. Among the patients with good results are included the cases of chronic pancreatitis who are relieved from symptoms related to biliary obstruction, but maintained symptoms due to pancreatitis. Eight patients with fair results have had brief episodes of cholangitis which responded to antibiotic and corticosteroid treatment. Finally, stricture of hepaticojejunostomy requiring reoperation developed in nine patients (Table 4). Seven patients surviving to reoperation have been followed 1–4 years and have generally done well. No significant difference in the immediate and long-term results was found to be in patients undergoing hepaticojejunostomy and in patients submitted to Hepp procedure.

Discussion

Hepaticojejunostomy has been used for many years generally to overcome iatrogenic stricture of CBD.[3,23] Conversely, there was a wide variation in the indications for

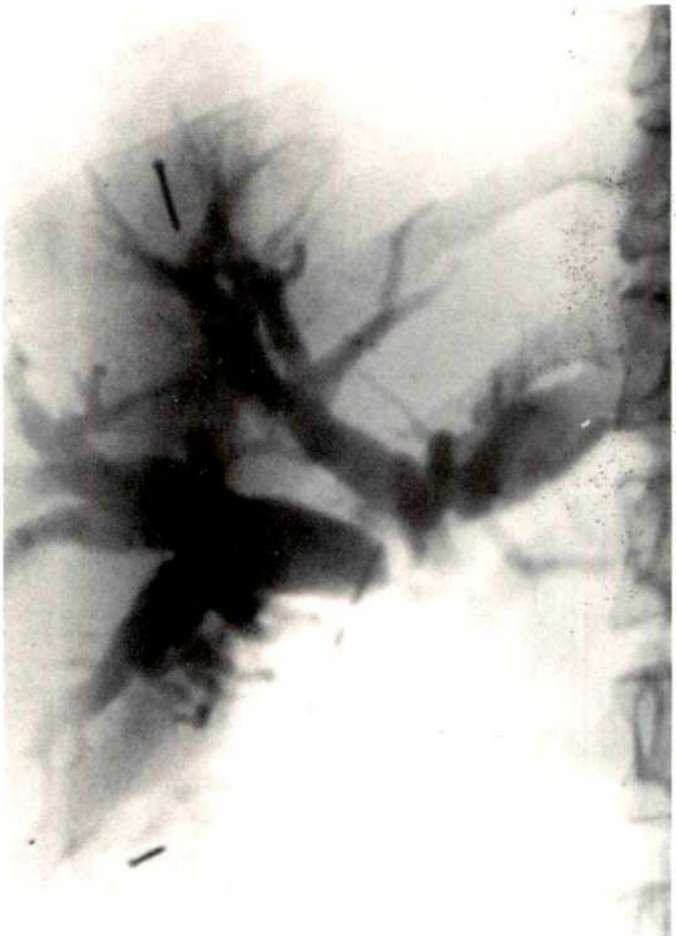

FIG. 3. Cholangiogram obtained at operation in a patient with biliary stricture due to the complete excision of CBD during cholecystectomy.

choledochoduodenostomy, including stricture or inflammatory stenosis of CBD, stenosis at the sphincter of Oddi, chronic pancreatitis and choledocholithiasis with markedly dilated duct.[8,17,22]

On the basis of accumulated experience, a critical reappraisal of these indications is needed.

The current criticisms against an enlargement of indications of hepaticojejunostomy are: 1) the high operative mortality; 2) the difficulty in technical performance; 3) the risk of peptic ulcer; 4) the inadequate long-term results.

The review of the literature shows that the mortality rate of hepaticojejunostomy ranges from 3.7%[10] to 6.6%.[11] In our 131 patients submitted to 140 hepaticojejunostomies the death rate was 4% and has dropped to 3% in recent years with increasing experience in the technical details. Consequently, the operative risk of hepaticojejunostomy is about the same of choledochoduodenostomy (0–8%, with a mean of 3%).[22]

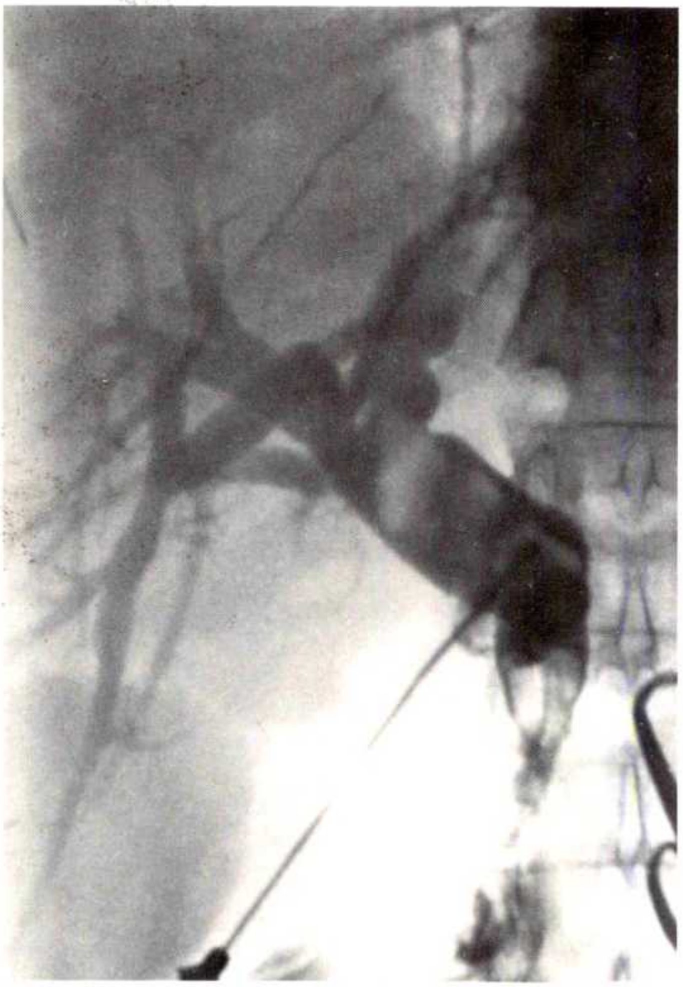

FIG. 4. Operative cholangiogram in a patient with choledocholithiasis. The entire ductal system is distended, with marked enlargement of CBD (over 2 cm in diameter).

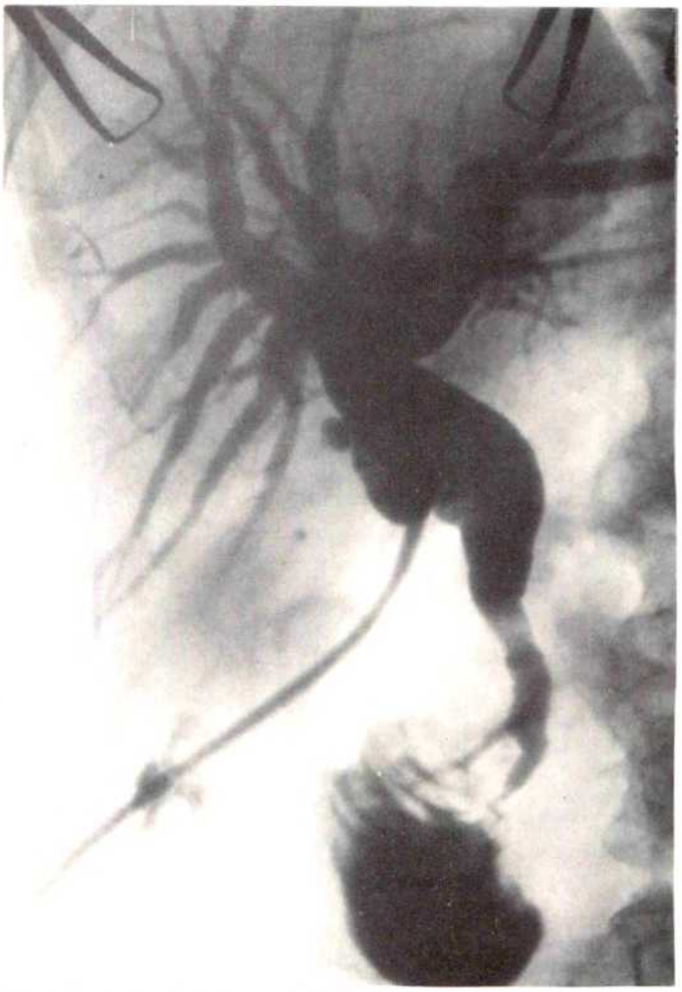

FIG. 5. Operative cholangiography showing a marked enlargement of the proximal ductal system, and a wide stenosis of the lower portion of CBD in a patient with chronic pancreatitis.

As for technical difficulties, it should be emphasized that the only difference between end-to-side choledochoduodenostomy and hepaticojejunostomy is the preparation of Roux-en-Y jejunal limb. This is at present currently employed in several surgical procedures and is easily and rapidly performed with the increasing practice. Conversely, the Hepp procedure poses technical problems that are related to the severity of lesions. In any case, the management of these conditions requires major surgery. In addition, the inverse correlation between technical difficulties reported in the operative notes and the eventual result, has been suggested by many surgeons.[11,25] The practical advantages of hepaticojejunostomy compared with choledochoduodenostomy are that it is most flexible in its application particularly when dealing with strictures high in the hilum of the liver, that a possible restenosis can be more easily managed, and that if a fistula does occur, it is much more difficult if it occurs in the duodenum than in the defunctionalized jejunal limb.

Recently, it has been suggested by many surgeons[13] that

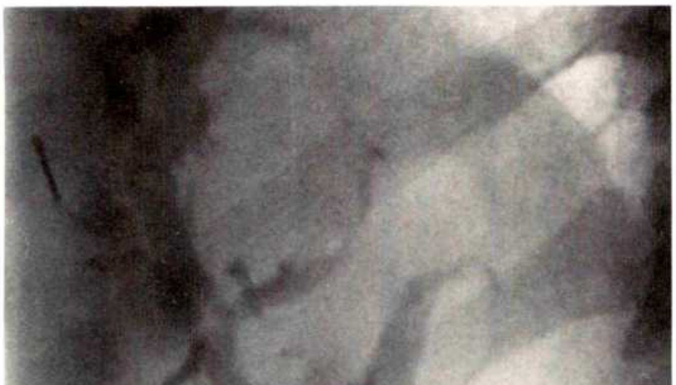

FIG. 6. Operative cholangiogram in a patient with choledochitis. Note the generalized enlargement and thickening of the bile ducts, the wide stenosis of the distal common duct, and a stone impacted in the ampulla.

the diversion of alkaline bile from the duodenum will result in an increased incidence of peptic ulcer disease. A review of the literature shows that the incidence of peptic ulcer disease in patients treated with a Roux-en-Y hepaticojejunostomy ranges from 8%[25] to 22%[1] of the cases. In the experience of Lindenauer[11] hepaticojejunostomy was not associated with an increased incidence of peptic ulcer disease. This evidence is supported by the present series, showing that only 4 patients (5%) of the total of 80 cases reviewed and evaluated, developed peptic ulcer disease. The diagnosis of peptic ulcer was established radiologically, and three patients were treated medically with good results, while the fourth required a vagotomy and pyloroplasty. Despite our findings, we agree with others[13] that a complete evaluation of peptic ulcer potential is mandatory, and postoperative protection of patients with a proclivity to ulcer disease is essential. Moreover, in patients with peptic ulcer demonstrated before operation, vagotomy and pyloroplasty should be always associated to hepaticojejunostomy.

Finally, the effectiveness of hepaticojejunostomy is indicated by the evaluation of the long-term results. Usually, the absence of cholangitis for two or three years is consistent with a good result in the majority of instances.[2,7] In fact, the presence of cholangitis is diagnostic of some degree of biliary obstruction,[11] and is an excellent indication that an inadequate anastomosis is present.

Good or fair results were obtained from 75–80% of the patients submitted to choledochoduodenostomy.[5,13,17] In the present series the long-term results were excellent or good in 79% of the cases and fair in 10%. Satisfactory results in 87% of the patients treated are reported by Lindenauer,[11] and Way and Dunphy.[25] In reviewing over 900 cases with benign obstruction of CBD, Warren[24] emphasized the good results of hepaticojejunostomy that provides better chance of a definitive cure than ent-to-end anastomosis. This is in keeping also with the findings of White[26] and of Longmire and Rongel.[12]

Recently, it has been increasingly suggested that choledochoduodenostomy is the best approach to remove CBD stones and to overcome biliary obstructions.[4,7,14]

However, it is clear that disadvantages of this procedure are: 1) the cul-de-sac of the intrapancreatic portion of CBD which is an important factor of stasis and plays a determinant role in developing choledochitis; 2) the reflux of duodenal contents which favours the occurrence of "ascending" cholangitis; and 3) the management of possible restenosis which poses technical difficulties.

Nevertheless, it has been emphasized that these adverse effects of choledochoduodenostomy may be limited making an adequate stoma, at least 2.5 cm in diameter, to avoid stasis and cholangitis.[4,8] Moreover, despite the reflux of duodenal contents into CBD, no increased incidence of

TABLE 2. *Procedures Performed in 119 Patients Before Hepaticojejunostomy*

First Procedure	No. of Cases	
Cholecystectomy	77	
Cholecystectomy, choledochotomy and Kehr-tube	11	
Cholecystectomy and papillostomy	10	
Cholecystectomy and choledochoduodenostomy	8	
Cholecystectomy and choledochotomy	8	
Gastrectomy	5	
		119
Subsequent Procedures		
Papillostomy	31	
Choledochoduodenostomy	19	
Hepaticojejunostomy	14	
Choledochotomy and Kehr-tube	12	
End-to-end anastomosis	2	
		78
Total	197	

In 12 patients hepaticojejunostomy was performed as first procedure

TABLE 3. *Long-term Results of 80 Patients Submitted to Hepaticojejunostomy*

	CBD Stricture (51 cases)		CBD Lithiasis (29 cases)		Total (80 cases)	
	No. of cases	%	No. of cases	%	No. of cases	%
Good	40	78.4	23	79.1	63	78.7
Fair	5	9.8	3	10.3	8	10
Poor	6	11.8	3	10.3	9	11.3

cholangitis in absence of obstruction and stasis is reported.[7,14] In addition, the presence of "blind" segment of CBD between anastomosis and duodenal papilla is not considered of practical surgical significance.[14]

In spite of these data, the present review shows that choledochoduodenostomy is unadvisable because of the hazards associated with the pathophysiologic consequences of the procedure. Of 131 patients submitted to hepaticojejunostomy, eight had previously a cholecystectomy and choledochoduodenostomy and 19 a choledochoduodenostomy. Of the total of 47 patients who underwent choledochoduodenostomy in our Clinic before 1960, two died (4.5%) and nine (20%) required hepaticojejunostomy. Most of these patients developed cholangitis, recurrent stones and obstruction of the CBD. Indications for choledochoduodenostomy were choledocholithiasis (28 cases), stricture by surgical injury (12 cases), stenosis of the sphincter (four cases), wide CBD stenoses (four cases) and chronic pancreatitis (one case). This evidence is in keeping with the findings of Jones,[9] Olivier,[16] and Smith[18] who have stated that choledochoduodenostomy should only be used if no other alternative is possible. Consequently, in our experience at present choledochoduodenostomy is performed only in patients submitted to gastrectomy, in whom duodenal loop is excluded from the enteric contents and provides excellent protection against reflux. Moreover, an end-to-side anastomosis between CBD and duodenum is always employed to avoid the so-called sump syndrome in that the cul-de-sac accompanying choledochoduodenostomy is excluded from the biliary flow.

All the conditions which indicate choledochoduodenostomy in our opinion may be at best treated with hepaticojejunostomy or sphincteroplasty. In patients with iatrogenic stricture, choledocholithiasis or stenosis at the sphincter of Oddi with markedly dilated duct, wide stenosis of CBD and choledochal cyst, a routine hepaticojejunostomy is the procedure of choice. Conversely, in patients with choledocholithiasis or stenosis at the sphincter of Oddi and diameter of CBD less than 1.5–2 cm spincteroplasty is the preferred operation.[20] In these cases

TABLE 4. *Patients Reoperated for Stricture of Hepaticojejunostomy*

Sex	Age	Previous Operations	Indication for Hepaticojejunostomy	Result After First Hepaticojejunostomy	Result After Second Hepaticojejunostomy
F	44	cholecystectomy (1958) choledochoduodenostomy (1960) Kehr-tube (1961)	stricture of choledochoduodenostomy	cholangitis 2 months after	died in fifth post-operative day for renal hepatic failure
F	34	cholecystectomy (1958) choledochotomy and Kehr-tube (1960)	biliary fistula	cholangitis 1 month after	died in third post-operative day for cardiac failure
M	28	cholecystectomy (1962) choledochotomy and Kehr-tube (1963) choledochoduodenostomy (1963)	stricture of choledochoduodenostomy	cholangitis 6 months after	symptom-free at 1 year followup
F	39	cholecystectomy (1964) choledochotomy and Kehr-tube (1966)	recurrent lithiasis	cholangitis 1 year after	symptom-free at 2 years followup
M	56	cholecystectomy and papillostomy (1966)	recurrent lithiasis	cholangitis and stones 1 year after	symptom-free at 3 years followup
F	46	cholecystectomy (1968) choledochoduodenostomy (1968)	stricture of choledochoduodenostomy	cholangitis and biliary fistula 4 months after	symptom-free at 3 years followup
F	30	cholecystectomy and choledochoduodenostomy (1968)	stricture of choledochoduodenostomy	cholangitis 5 months after	symptom-free at 4 years followup
F	55	cholecystectomy (1969)	complete excision of CBD	cholangitis 8 months after	symptom-free at 2 years followup
M	35	cholecystectomy (1970)	recurrent lithiasis	cholangitis 1 year after	symptom-free at 2 years followup

sphincteroplasty provides at the same time: 1) a more rationale treatment of papillitis, ampullary stones and chronic pancreatitis related to gallstones; 2) an easy and safe approach to the CBD for exploration and stone removal; and 3) a prevention of the biliary stasis and recurrence of stones. However, when a markedly dilated duct is present sphincteroplasty is not effective in preventing biliary stasis because of the discrepancy between CBD size and papillary opening, and therefore hepaticojejunostomy is required.

In conclusion, several conditions which indicated choledochoduodenostomy may be at best treated with hepaticojejunostomy, which provides a low mortality (3%) and satisfactory long-term results in 89 per cent of the cases. It is not adequate treatment for pancreatitis related to alcoholism, that should be treated with denervative, derivative or resective procedures according to the circumstances.[21] On the basis of accumulated data, a limitation of the extent of indications of choledochoduodenostomy seems to be advisable.

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The Ability of an Elemental Diet to Support Nutrition and Adaptation in the Short Gut Syndrome

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85% enterectomy or jejunal biopsy was randomly carried out on 80 male Sprague-Dawley rats, 300–350 gm. After recovery, rats in each group were randomly fed either elemental diet (ED) or rat chow. All rats were sacrificed 8 weeks postoperatively. Biopsied rats gained more weight with ED than chow (22% vs. 18%; p < .01). Resection produced greater weight loss than biopsy (p < .01) and slower gain (p < .01). The failure to gain was most marked in ED rats, significantly less than in the chow group (p < .05) by week two. A fall in hemoglobin, protein and albumin was seen: neither the fall nor difference between the groups was significant (p > .05). Enterectomized chow rats ate 22% more than their controls (p < .05), whereas the ED group ate 1[illegible]% less (p > .05). Increase in bowel length after resection, equally divided between jejunum and ileum, was 21% with ED and 26% with chow. Gut diameter after resection increased 104% and 98% with chow and ED, respectively. Villus height increased 35% in the jejunum of both enterectomized groups and 85% and 78% with chow and ED, respectively, in the ileum. Changes in gut length, diameter and villus height are significant in each group (p < .01) but not between groups (p > .05).

UNTIL ADAPTIVE CHANGES consisting of lengthening of villi, thickening of the intestinal wall, dilatation of the gut and slowing of motility, have taken place, the patient with short gut syndrome is unable to tolerate enteral feeding. Yet Wilmore and associates[9] have demonstrated the importance of nutritional support during this adaptive stage, showing an improved survival rate in puppies whose nutritional needs following massive bowel resection were met by intravenous hyperalimentation. The surviving dogs also demonstrated greater lengthening of villi, wider gut diameter, more hypertrophy and earlier cessation of diarrhea in the group initially supported by intravenous hyperalimentation. Techniques of intravenous hyperalimentation have enabled many more patients to survive the adaptive stage until oral feedings can be tolerated. These techniques, however, carry a finite rate of serious complications, increasing with lack of familiarity. The search for alternate methods of nutritional support therefore seem appropriate.

Voitk and associates[8] have recently reported on the successful use of an elemental diet for nutritional support in 8 patients with short gut syndrome. The validity of their conclusions may be questioned because of the heterogeneity of the small group and the absence of controlled data. The relative rarity of the condition along with the wide variation in clinical presentation makes an accumulation of conclusive clinical data difficult. In laboratory studies, Bury[1] was unable to demonstrate any advantages of elemental diet over "normal" rat chow during the adaptive phase in enterectomized rats. Touloukian and co-workers[5] demonstrated decreased weight gain in elemental diet fed enterectomized rats when compared to controls. The short gut syndrome in this latter study however, was so mild (66% mid-gut resection) that no growth disturbance was evident with normal food when compared to non-resected rats. Growing animals, where adaptation is the norm, were used by Wilmore *et al.*, and to some extent by Bury.

The present study, therefore, was designed to investigate the applicability of the elemental diet in the short gut syndrome using a model more closely simulating the clinical situation. A sufficient enterectomy to cause major nutritional problems was done, and adult animals were used to eliminate the natural ability of adaption present during growth and development.

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Method

Eighty male Sprague-Dawley rats weighing 300–350 gm were randomly divided into four groups.

Group I. (Biopsy-chow) A 2 cm jejunal biopsy and end-to-end anastomosis were done. Postoperatively the rats were fed laboratory rat chow (6% Fat, Rat/Mouse Feed, Teklad Inc.) *ad lib.*

Group II. (Biopsy-diet) Biopsy similar to Group I was done and postoperatively the rats were fed an elemental diet (Flexical, Mead-Johnson Co. of Canada) *ad lib.*

Group III. (Resection-chow) An 85% enterectomy of small gut between ileocecal valve and ligament of Treitz was done with an end-to-end anastomosis between a constant 5 cm length of terminal ileum and a variable length of proximal jejunum. Rat chow was fed postoperatively as in Group I.

Group IV. (Resection-diet) An 85% enterectomy was done as in Group III and elemental diet given as in Group II.

Hemoglobin, albumin and total protein were determined at the time of operation and at sacrifice, 8 weeks later. A daily record was kept of weight, food and water consumption, and amount and character of stool. At sacrifice gut length and diameter were measured and comparative biopsies submitted for histologic study. These were opened longitudinally, pinned to cardboard, fixed in gluteraldehyde, sectioned perpendicularly, stained with hematoxylin and eosin and examined microscopically. Villus height was determined by the average height of 5 tallest villi in one arbitrarily chosen high power field.

Table 1 lists the relative composition of the chow and elemental diet. Detailed composition of chow is available on request and has been published for Flexical.[7] Statistical comparisons were done by analysis of variance.

Results

Morbidity and Mortality

All animals appeared healthy and showed no sign of disease at the time of operation. Animals showing subsequent morbidity, or who died, were excluded from the above analyses. In consideration of morbidity and mortality, those resulting from errors in technique have been excluded. Three animals were destroyed to prevent spread of a contagious inner ear infection; these have not been included in the mortalities, but have been considered as examples of morbidity. All mortality within 48 hours of operation has been excluded, assuming this to be related to technical aspects of the operative procedure rather than the form of nutrition. Intercurrent infections have been included in the consideration of morbidity and mortality, as it is difficult to differentiate between that infection which occurs by chance and that arising because of an animal's susceptibility to it, secondary to its nutritional state or therapy. Incidence is expressed as a per cent of those animals per group left for consideration according to the above guide lines (Table 4).

TABLE 1. *Relative Composition of Chow and Elemental Diet (Gm % Dry Weight)*

	Chow	Diet
Protein	25.33	9.50
Fat	6.35	14.22
Carbohydrate	28.0	67.31
Fiber	3.73	0.02
Moisture	10.30	2.30
Calories	275.0	432.0

Guided by by the foregoing attempt to exclude unrelated causes of morbidity and mortality, the corrected morbidity (Table 4) is seen to be highest in the elemental diet fed rats both in the biopsy and resected groups. The highest incidence of morbidity (33%) occurs in Group IV (resected-diet).

Mortality does not show a similar increase in Group II (biopsy-diet), but also has the highest incidence (15%) in Group IV.

Because of the somewhat arbitrary selection produced by the effort of correction, no attempt was made to attach statistical significance to these differences. It is of interest to note that when all morbidity and mortality is considered, regardless of cause and without attempt at correction, the trend noted above persists: the worse prognosis is still most markedly seen in Group IV (40% mortality vs 20% in Group III and exactly the same incidence of comparative morbidity).

Nutritional

Weight changes for each group are shown in Fig. 1. The arrival weights were similar in each group ($p > 0.05$) with a mean weight of 324 ± 1.8 gm for all the rats. All groups gained an average of 3% over one week before operation. This gain was significant ($p < 0.01$) and resulted in groups with highly similar immediate preoperative weights (Fig. 1; $p > 0.05$; $M \pm SEM = 336 \pm 1.5$ for all the rats). Both Group I (biopsy-chow) and Group II (biopsy-diet) rats lost 8% of their preoperative weight ($p < 0.01$) by the second postoperative day and started to gain thereafter. Group I rats regained their preoperative weights by the second postoperative week, and thereafter continued a steady weight gain. At eight weeks the average gain was 18% above preoperative weight.

The pattern of Group II (biopsy-diet) rats was similar to that of Group I except that the weight gain after operation was faster and greater than that observed for Group I. This difference between the groups became significant ($p < 0.01$) by the 7th postoperative week. They had gained 24% over their preoperative weight when killed.

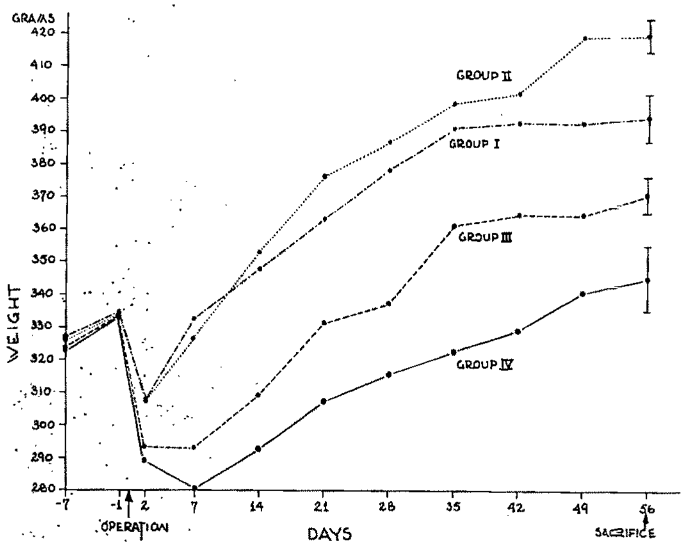

FIG. 1. Weight curves for all groups of rats over the study period. Each point represents a statistically significant change ($p < 0.01$) from that before or after within any group, except for the last four weeks for Groups I and III which have reached a pleateau of very slow gain. Preoperatively there are no significant differences between the groups. Two days postoperatively the biopsied rats (Group I and II) weigh significantly more than the resected ones (Groups II and IV; $p < 0.01$) and this difference persists throughout. The difference between Groups I and II does not become significant ($p < 0.01$) until day 49, but persists thereafter. Groups II and IV become significantly different ($p < 0.01$) by day 14, and this difference also persists. The standard error of the mean is shown only for day 56. That also represents the day when this determination was widest for all groups.

Rats in Groups III (resection-chow) and IV (resection-diet) lost 13% and 15% ($p > 0.05$), respectively, of their preoperative weight by the second postoperative day. Both resected groups reached their lowest mean weight one week after operation, losing a further 2%, and began to gain slowly thereafter. Group III (resected-chow) rats had regained their preoperative weight by four weeks after operation and when killed weighed 10% more than their preoperative weight ($p < 0.01$). Thus, they had gained 8% less than their controls (Group I; $p < 0.01$).

As opposed to the diet fed rats in the biopsy group, whose weights exceeded their chow fed peers, diet fed rats in the resected group (Group IV) showed the poorest weight gain of all. They did not reach their preoperative weight until the seventh postoperative week, and at sacrifice (8 wk) had exceeded it by only 2%, an insignificant difference. Their final weights were significantly less than those of both resected-chow (Group III; $p < 0.01$) and biopsy-diet (Group II; $p < 0.01$) groups. The difference between Groups II and IV became significant ($p < 0.01$) by the second postoperative week.

Analysis of food consumption revealed that the pre and postoperative food consumption of Group I (biopsy-chow) rats was similar, and was indistinguishable from that of the preoperative Group III (resected-chow) ($p > 0.05$). Following resection, however, Group III rats ate 22% more than their biopsied peers (Group I; $p < 0.01$). In contrast to this rats offered elemental diet ate 10% less after resection than after biopsy. This difference did not appear statistically significant ($p > 0.05$) when considering daily food consumption, but did begin to assume significance ($p < 0.05$) if total postoperative food consumption was considered.

The only differences in water consumption noted consisted of markedly reduced drinking in groups fed the liquid elemental diet. Otherwise no difference in the pattern of drinking between the groups could be seen.

By the gross method of inspection to quantitate stool, no difference in amount between groups was detected. All resected animals showed diarrhea for a few days postoperatively, but by one week stool was generally formed. Of five resected animals with persistent diarrhea, four were in the elemental diet fed group (Group IV).

Preoperative hemoglobin concentration for all rats was 17.4 ± 0.9 gm % (M ± SD) with no difference between groups. By sacrifice the hemoglobin had risen less than 0.05 gm % in the biopsy groups, fallen less than 0.05 gm % in Group III (resection-chow), and fallen 1.2 gm % in Group IV. None of these changes within the groups was of statistical significance ($p > 0.05$). The differences between groups at sacrifice, however, were significant. Groups I, II, and III did not differ significantly from each other, but Group IV (resection-diet) had a significantly lower hemoglobin level than both biopsy groups ($0.01 < p < 0.05$). The value was just approaching being significantly less than Group III (resection-chow), p being slightly greater than 5%.

Serum protein concentration for all rats was 5.9 ± 0.5 gm % (M ± SD) preperatively, with no significant difference between the groups. This concentration fell by less than 0.5 gm % by sacrifice (8 wk) in Groups I, II, and IV, p in each case being greater 5%. Group III (resection-chow) rats alone saw a significant drop, 5.9 gm % to 5.2 gm % ($0.01 < p < 0.5$); the differences between the groups were not statistically significant at the time of sacrific.

Preoperative serum albumin for all rats was 2.1 ± 0.3 gm % (M ± SD) with no difference between the groups. There was a non-significant drop in this value in Groups I, II, IV and Group III (biopsy-diet) showed an insignificant rise. At sacrifice the only significant difference between groups was between albumin values of 1.7 and 2.2 in Groups I (biopsy-chow) and II (biopsy-diet), respectively ($0.01 < p < 0.05$).

Some of the nutritional changes are summarized in Table 2.

Adaptive

Preoperative length of small gut from ileocecal valve to ligament of Treitz was 81 ± 10 cm (M ± SD), varying 53-103. A few rats were not properly fasted, and their full gut measured more than empty ones, producing the slight skew. There was no difference in length between the groups.

TABLE 2. *Per Cent Change of Nutritional Parameters**

	Weight	Hemo-globin	Total Protein	Albumin
Group I	(18)	29	−7	−19
Group II	(24)	17	−8	0
Group III	(10)	−11	(−12)	−22
Group IV	2	−40	−7	−9

* Significant changes (analysis of variance; $p < 0.05$) within groups bracketed.
Significance of changes between groups discussed in text.

Following operation, whether biopsy or 85% enterectomy, an increase was noted in the bowel length. In the biopsy groups the short segments of proximal jejunum only were measured. Group I (biopsy-chow) showed an 18% increase in length, whereas Group II showed a 21% length increase of the jejunal segment. Length increases of the jejunal segments in resected rats were 18% and 26% for Groups III and IV, respectively. Total gut length increases for Groups III and IV were 21% and 26%, respectively, and increases in the ileal segments measured 25% and 21% respectively. All these length increases were significant within the groups ($p < 0.01$), but no significance was detected in the differences between groups ($p > 0.05$).

No significant difference in diameter was detected in non resected guts (Groups I and II) whereas the diameter doubled ($p < 0.01$) in all resected animals with no detectable difference between Groups III and IV. There was no appreciable difference of diameter between jejunum and ileum in any group at any stage.

Before operation average villus height in the jejunum was the same for all groups. Following biopsy a 9% and 20% increase in villus height of the jejunum was seen with chow and diet, respectively. Only the increase with diet (Group II) was statistically significant ($p < 0.01$); there was no significant difference in the taller villi between these two groups. Following resection, both chow and diet produced a 60% increase ($p < 0.01$) in jejunal villus height; this was significantly more ($p < 0.01$) than the increase seen with biopsy for both chow and diet.

Villus height in the ileum was measured for Groups III and IV only, Groups I and II undergoing a jejunal and not ileal biopsy at operation. For comparison purposes the average preoperative villus height of Groups III and IV was used as the control value for Groups I and II. By this determination, biopsy produced a 6% increase in ileal villus height with chow ($p > 0.05$) and a 6% decrease ($p > 0.05$) with diet. These differences between the two groups were not significant ($p > 0.05$). Following resection an 84% ($p < 0.01$) and 78% ($p < 0.01$) increase in villus height of the ileum was seen with chow and diet, respectively. The difference between these two groups was not significant ($p > 0.05$), but both groups differed significantly ($p < 0.01$) from the increases in Groups I and II.

Some of the adaptive changes are summarized in Table 3.

Discussion

The data show that elemental diet can support nutrition in the adaptive phase of the short gut syndrome, but less well than normal food (chow). Resected rats fed elemental diet lost more weight and gained more slowly than their chow-fed counterparts. Although it seemed that in this group hemoglobin levels fell more and protein and albumin levels less than those of the chow fed group, these changes were not statistically significant.

Diarrhea seemed to persist longer in the diet fed group with short gut syndrome and these rats also had the highest incidence of morbidity and mortality. Although some of this stems from unrelated causes a rough correlation between morbidity and mortality and nutritional status must exist. Examination of only that morbidity and mortality related to difference in diet confirmed that elemental diet fed rats with short gut syndrome fared less well than those on chow. No deaths were directly related to malnutrition or starvation.

Failure to support nutrition in the short gut syndrome does not stem from inferiority of elemental diet as food for rats. Rats subjected to biopsy alone gained significantly more weight when eating elemental diet instead of chow. This demonstrates that under "normal" circumstances rats eat sufficient amounts of elemental diet. Generally, polyphagia is a feature of the short gut syndrome[6,9] and was seen in this study in the chow fed rats. Rats with short guts fed with elemental diet, however, did not exhibit polyphagia. In fact, they ate less than those subjected to biopsy, although this difference only bordered on statistical significance. Thus, rats with short guts do not seem either

TABLE 3. *Per Cent Change of Adaptive Parameters**

	Gut Length			Gut Diameter		Villus Height	
	Total	Jejunum	Ileum	Jejunum	Ileum	Jejunum	Ileum
Group I	Not measured	(18)	Not measured	0	0	9	6†
Group II	Not measured	(21)	Not measured	0	0	(20)	−6†
Group III	(21)	(18)	(25)	(100)	(100)	(60)	(84)
Group IV	(26)	(26)	(21)	(100)	(100)	(60)	(78)

* Significant changes (analysis of variance; $p < 0.05$) within group bracketed. Significance of changes between groups discussed in text.
† Preoperative control value not obtained; average preoperative value for Groups III and IV used for control (see text).

willing or able to consume as much elemental diet as they "should" for nutritional support, and may in fact consume less than "normal" in this situation. The nutritional shortcomings noted in the elemental diet fed short gut rats are related at least in part to the inability or unwillingness of resected rats to eat enough diet, rather than to qualitative inadequacy of the elemental diet. The mechanism behind this decreased dietary intake is not apparent from the present study. Because of unmeasurable but probably significant differences in spillage between the liquid elemental diet and solid chow pellets, consumption differences between the two dietary groups could not be analysed reliably.

Adaptive changes take place with elemental diet, but the diet offers no advantage over normal food (chow) in the extent or degree to which they take place. In the normal setting (biopsy) elemental diet produces more changes in the jejunum than in the ileum and jejunal changes are greater with elemental diet than chow. Being predigested, elemental diet can, at least theoretically, be totally absorbed high in the proximal gut, and therefore any changes that are brought about may reasonably be expected in the proximal bowel. Food requiring digestion and containing wastes may be expected to bring about effects more evenly distributed throughout the gut. Elemental diet is also hypertonic. Because of this it may result in a larger fluid load in the proximal bowel, which may explain why the anastomotic leaks (two) were limited to elemental diet fed short gut rats.

Classically, adaptive changes are limited to or most marked in, the terminal ileum.[1,8] In this experiment no difference could be discerned between ileal and jejunal changes. Similar findings were noted by Touloukian and Mitruka.[5] In our study this may result from taking biopsies less than 5 cm from the anastomosis; gross inspection at the time of sacrifice showed more change in the ileum than the duodenum, with progressive distal enlargement. Bury noted most marked changes immediately proximal to the anastomosis, without evidence of obstruction.[1]

In response to biopsy and end-to-end anastomosis, the jejunal segment increased in length equally in both dietary groups, increase being indistinguishable from that seen after resection. The role of possible obstruction at the anastomosis is not clear, for anastomotic diameter was not measured. However, if all changes resulted from obstruction, changes in diameter should also be expected. These were not observed, suggesting that there was no obstruction. Changes in response to minimal tissue removal and anastomosis have been documented before: Loran and Crocker[4] showed that epithelial cell turnover increases and remains elevated following 10% enterectomy.

Our study also sheds some indirect light on the stimulus for adaptive change. Dowling *et al.*[3] have demonstrated that dietary bulk alone does not lead to adaptive changes in the short gut syndrome. Our study confirms the converse of this, by showing that the absence of bulk (elemental diet) does not prevent the appearance of adaptive changes. Doris, working in our laboratories with a dog preparation of simultaneous short gut and short Thiry-Vella fistula, demonstrated the lack of adaptive changes in the fistula and concluded that intraluminal contents rather than neurohumoral factors were responsible for the adaptive changes.[2] The combination of the above findings[2,3] with ours suggest that the intraluminal contents responsible for adaptive changes are likely to be some of the endogenous gastrointestinal secretions in abnormal sites or quantities, rather than exogenous dietary components. The latter merely allow these changes to come about by providing the necessary nutritional building blocks.

TABLE 4. *Incidence of Mortality and Morbidity (Corrected)*[*]

	Group I		Group II		Group III		Group IV	
	Number	%	Number	%	Number	%	Number	%
Morbidity	1	6	3	16	1	7	4	33
Mortality	1	6	1	5	0	0	2	15

[*] See text for explanation.

Unfavorable conclusions regarding elemental diet, suggested by this study, require qualification before unconditional acceptance. We have shown that resected rats did not consume "sufficient" amounts of elemental diet. This situation presumably does not arise in the clinical setting, for here it is generally recommended that elemental diet be administered at a controlled rate by nasogastric tube.[6] In this experiment full strength diet was used from the outset; in clinical practice the gut is allowed to accept this osmotic and fluid load by gradual increments from dilute to full strength, and then by a slow increase in volume.[7] Furthermore, elemental diet has been recommended as particularly useful in situations where normal food is not tolerated by the acutely shortened gut. This was not comparable to the experimental situation, where resected rats did not have difficulty tolerating chow, and managed to gain weight on it. Finally, quite often the clinically encountered short gut syndrome is complicated by the loss of terminal ileum and ileocecal valve, compounding problems of diarrhea, fluid and electrolyte balance and absorption of fat and bile salts. Terminal ileum and ileocecal valve were retained in this model in order to prevent excessive deaths from diarrhea and to enable the study of adaptive changes in the terminal ileum where they have been described as most marked.

Nonetheless these differences between the model and the clinical setting are minimal and the model is a satisfactory approximation of the clinical situation being tested. Therefore the results of this experiment give some real cause for hesitancy in recommending the use of elemental diet in the adaptive stage of the short gut syndrome. Such recommendations are based largely on anecdotal and uncontrolled experience with heterogenous patients.[8] This study serves to point out the suitability and importance of the laboratory in checking out initial clinical impressions as well as the need for controlled clinical trials before a new mode of therapy can be advocated with certainty. Further studies with alterations of the described model should be undertaken while the results of controlled clinical trials of this relatively rare entity are awaited.

Conclusions

1. Elemental diet can support rats with short gut syndrome.
2. Nutritionally it is inferior to normal food (chow) in this setting, although superior in the normal (biopsy) situation.
3. Elemental diet offers no advantages over normal food in bringing about adaptive changes.
4. These findings seem related to the refusal of resected rats to ingest "sufficient" amounts of diet.
5. Intraluminal dietary factors, particularly dietary bulk, do not seem to stimulate or to determine the degree of adaptive changes.
6. There is reason to question the usefulness of elemental diet in clinical short gut syndrome; further experimental and clinical studies are warranted.

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The Differentiation of Primary Hyperparathyroidism From the Hypercalcemia of Malignancy

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The presence of hypercalcemia in patients with known cancers may be due to the cancers themselves, or to co-existing primary hyperparathyroidism. The differentiation of primary hyperparathyroidism from the hypercalcemia of malignancy is important since the relief of distressing symptoms and prevention of hypercalcemic crises and renal failure can be accomplished relatively easily by parathyroid surgery in the former condition, and only with difficulty, at times, with fluids and drugs in the latter condition. The histories of three recent patients are presented, which demonstrate the difficulties inherent in the differentiation of these conditions. These patients were ultimately found at operation to have primary hyperparathyroidism in addition to malignancies of the cervix, adrenal gland and kidney. In our experience the following have been helpful in establishing a diagnosis: history of hypercalcemia prior to development of cancer, the type of cancer itself, the effect of cancer therapy on the hypercalcemia, and selective venous sampling with radioimmunoassay for parathyroid hormone.

In the management of patients with hypercalcemia one must differentiate between parathyroid adenoma or hyperplasia and a variety of other diseases that can cause elevations in serum calcium. It is known that certain cancers can produce hypercalcemia in individual patients and this has been termed the hypercalcemia of malignancy, pseudohyperparathyroidism or ectopic hyperparathyroidism. The differential between primary hyperparathyroidism and hypercalcemia of malignancy can be very difficult since the carcinoma may be occult. This differential diagnosis must be considered even in patients with a known cancer. In other words, in the patient with an active cancer and hypercalcemia, is the elevated calcium due to the cancer or to a coexisting parathyroid adenoma? This is not merely an academic question. The symptoms caused by the high calcium levels may cause the patient great discomfort and may actually be more immediately life threatening, at times, than the cancer itself. There are reports of patients with neoplastic diseases dying as a result of hyperparathyroid crises due to uncontrollable hypercalcemia.

The management of hypercalcemia of malignancy and primary hyperparathyroidism is obviously very different. In the former, fluid and drug therapy are often successful in managing the hypercalcemia, but in many patients management is extremely difficult. In the latter, operative exploration for primary parathyroid disease is generally successful and there are relatively few complications. With the low risks involved, operative explorations can be performed even in patients with debilitating diseases and in those in the later stages of cancer. We have had three patients recently with active cancers and coexisting primary hyperparathyroid disease. The management of these patients illustrates the problems involved in these conditions as well as an approach to the differential diagnosis.

Case Reports

Case No. 1: This 57-year-old female was admitted to the hospital on December 19, 1971 with a 5 month history of vaginal bleeding. Biopsies taken in the out-patient clinic several weeks earlier established the diagnosis of carcinoma of the cervix, Class II-B. The patient was also noted to be hypertensive. Among her other laboratory studies, the serum calcium was >15 mg%, phosphate was 1.4 mg%, and the alkaline phosphatase was 92.[*] An SMA-12 two months earlier in the clinic also showed a calcium of >15 mg%, a phosphate of 2.2 mg% and an alkaline phosphatase of 107. The carcinoma was treated by radium implantation.

The patient was re-admitted to the hospital on September 15, 1972 with a complaint of low back pain, easy fatiguability, and constipation. She also

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[*] Normal values at this hospital: calcium 8.5 to 10.5 mg.%, phosphate 2.5 to 4.5 mg.%, alkaline phosphatase 30 to 85 International units.

gave a history, as this time, of duodenal ulcer disease five years earlier. While she continued to have vaginal discharge, pelvic exams revealed only that which was considered a mild fibrosis of the vaginal cuff, felt to be due to radiation. Repeated serum calcium determinations during this time ranged 14.3–15 mg% and serum phosphate levels ranged 1.2–2.1%. With the presumptive diagnosis of primary hyperparathyroidism in this patient, a neck exploration was performed on September 28, 1972. A parathyroid adenoma weighing 1.2 gm was found at the lower left pole of the thyroid gland and was excised. Serum calcium levels rapidly dropped to the normal range, and when the patient was seen in the out-patient clinic during the next few months the serum calcium levels varied from 8.8 to 9.4 mg%. The patient noted improvement of the back pain and generally felt better. However, two months after parathyroid surgery she was re-admitted because of an obvious rectovaginal fistula. An abdominal exploration was carried out and considerable fibrosis and scarring were present in the pelvis. Numerous biopsies revealed only inflammed collagenous connective tissue, although a recurrence of the malignancy was strongly suspected. A diverting colostomy was performed. The patient was discharged in relatively good condition but returned to the hospital two months later in a moribund condition and expired. The patient's abdomen was markedly distended at the time of death, and although no autopsy was performed, it was obvious, clinically, that the patient had succumbed to her recurrent carcinoma. Serum calcium at the time of death was 7.4 mg%.

Comment

This patient lived for only four months after the parathyroid operation but had significant improvement of symptoms to justify this procedure. The presumptive diagnosis of primary hyperparathyroidism rather than hypercalcemia of malignancy was made because the patient had carcinoma of the cervix which does not commonly cause hypercalcemia, although there are several known instances of this occurring. In addition, the serum calcium levels did not drop to normal or near normal levels during the course of treatment of the cancer. At the time of the parathyroid operation, the cervical cancer appeared to be well controlled, but the calcium levels remained in an elevated range. Serum calcium levels of 14 or 15 mg% are potentially dangerous and parathyroid surgery could be justified even if the patient had been asymptomatic.

Case No. 2. This 36-year-old woman was admitted to the hospital on January 20, 1973 because of persistent hypertension. She had a 8 month history of diabetes and her weight had increased during the past few years from 135 to 200 pounds. On examination, her blood pressure was 240/160 and she appeared to have truncal obesity with a moon facies. Of significance in her laboratory tests was a generally low serum potassium, and elevated 17-hydroxy and17-ketosteroid levels. Repeated serum calcium determinations during this time ranged from 9.2 to 10.8 mg% and phosphate from 2.8 to 4.5 mg%. Elevated plasma cortisol levels, lack of suppression of steroid values with dexamethasone administration, unresponsiveness to ACTH stimulation, and evidence of an enlarged left adrenal gland on arteriography suggested Cushing's syndrome secondary to an adrenal tumor.

She was discharged from the hospital after this workup and was re-admitted on April 15, 1973 for further testing and definitive surgery. Adrenal venography was performed and the left adrenal vein appeared to be markedly enlarged with hypervascularity of the adrenal. Attempts to catheterize the right adrenal vein were unsuccessful. Two of three serum calcium determinations at this time were elevated slightly, as high as 10.8 mg%. On April 25, 1973, an abdominal exploration was performed revealing bilateral adenocarcinoma of the adrenals. A bilateral adrenalectomy was performed and a solitary metastatic nodule was excised from the liver. The patient tolerated surgery well and serum cortisol levels dropped below normal, postoperatively, although there was still serum cortisol present without administration of exogenous steroids. One serum calcium determination was obtained postoperatively and was 8.4 mg%. The patient was discharged on the thirteenth postoperative day, on medications including cortisone, 50 mg per day, which was later changed to prednisone, 10 mg per day.

The patient was re-admitted to the hospital on May 20, 1973 for a trial of therapy on o p' DDD. One serum calcium determination at this time was 10.4 mg%. She was discharged in 11 days but readmitted on June 27, 1973 because of vomiting, weakness, malaise, pain in her shoulder and a marked depression. Serum calcium levels at the time of this admission were >15 mg% and the alkaline phosphatase was also elevated. Plasma cortisol levels were at the upper limit of normal initially, but were found to be elevated later during this admission. Repeated serum calcium levels ranged from 11.5 to 15.2 mg% but gradually returned to normal levels of 9.9 mg% without therapy at time of discharge on August, 1973. A review of the patient's past records, revealed that she had high serum calcium levels intermittently over the previous four years, including a level of 11.7 mg% in April 1969.

She was again admitted to the hospital on August 21, 1973 because of continued nausea and vomiting, pain in the right shoulder, temporal headaches, general malaise and weakness, and extreme depression. Serum calcium at time of admission was 14.7 mg% and phosphate was 2.6 mg%. The serum alkaline phosphatase was again elevated. During the subsequent days, calcium levels rose as high as 17.4 mg%. These levels were controlled at first, with great difficulty, using massive infusions of fluids and sodium phosphate solutions. Although calcium levels dropped as low as 8.4 mg% during therapy, normal levels were extremely difficult to maintain. Because of the possibility of primary hyperparathyroidism, a neck exploration was performed on September 13, 1973. A small parathyroid tumor weighing 98 mg was discovered at the inferior pole of the right thyroid lobe, and was excised. Postoperatively, the calcium and phosphate levels returned to normal, although the alkaline phosphatase remained elevated. The patient had a dramatic response clinically, with marked relief of symptoms. Whereas preoperatively she had been emotionally depressed to the extent of becoming almost totally uncommunicative, postoperatively, within a few days, the patient was alert and cheerful. When seen in the out-patient clinic on January 29, 1974, the serum calcium level was 10.1 mg% and the phosphate level was 5.0 mg%.

Comment

This patient presented us with a difficult diagnostic problem. Although this is a rare tumor, there has been one report of a patient with adenocarcinoma of the adrenals, causing hypercalcemia.[21] In addition, it is very likely that this patient had additional metastatic cancer at the time of adrenalectomy. The decision to explore the neck for parathyroid disease was made, in part, on the history of elevated serum calcium levels as early as four years before discovery of her adrenal carcinoma. We were also impressed that there was only a transient response of the elevated calcium levels to the adrenal tumor surgery, at which time the bulk of the malignant tissue was removed. We felt that although the adrenal operation was not curative, all of the apparent tumor, including one liver nodule was removed and that a drop in calcium level, for a moderate period of time, would have been expected if the tumor was directly responsible for the hypercalcemia. In addition, there is another somewhat confusing factor involved. Adrenal steroids are often used to control hypercalcemia due to pseudohyperparathyroidism. This patient was producing, endogenously, high levels of adrenal steroids, but still maintained exceptionally high levels of serum calcium. Patients with Cushing's syndrome, even when caused by adrenal carcinoma, generally have normal or low serum calcium levels.[11] In fact, an acute fall in steroid levels after adrenalectomy in Cushing's syndrome may give rise to hypercalcemia. Primary hyperparathyroidism usually does not respond to the administration of adrenal steroids. We felt that there was a strong possibility that a parathyroid gland was hypersecreting independently, causing the elevated serum calcium levels. The operation was successful and the symptomatic response was remarkable.

An additional factor concerning this patient should be mentioned. Paloyan has suggested that the chronic use of thiazide preparations for treating hypertension may encourage the development of hyperparathyroidism.[16] This patient was treated with hydrochlorothiazide; however, she ultimately developed symptoms commonly seen in hyperparathyroidism, particularly musculoskeletal pain and depression, and these responded well to the excision of the parathyroid tumor. In Paloyan's experience, patients with prolonged thiazide administration and hypercalcemia did not suffer from the common complications of hyperparathyroidism.

This patient has already had adrenal and parathyroid diseases, possibly representing components of the multiple endocrine adenomatosis syndrome. She has not manifested signs of other endocrine disease up to this time.

Case No. 3. This patient, a 43-year-old female, was admitted to the hospital on February 10, 1973 with a complaint of headaches, hypertension, and a right abdominal mass. An intravenous pyelogram performed before the patient was admitted to the hospital revealed a markedly enlarged right kidney. The serum calcium level at time of admission was 12.1 mg% and the phosphate was 2.8 mg%. A repeat serum calcium was 12.4 mg% several days later. A right renal arteriogram showed a huge right renal mass with tumor staining and stretching of the vessels, suggesting a carcinoma. A metastatic roentgenographic survey and brain, lung, and liver scans were all normal. A right nephrectomy was carried out on February 15, 1973. While there was no evidence of capsule invasion or any lymph nodes invasion, and the renal vein was free of tumor, microscopic sections of this well-differentiated adenocarcinoma demonstrated some tumor cells in the small blood vessels and one small renal calyx showed some invasion. On the day after surgery the serum calcium dropped to 9.7 mg% but rose on the following day to 11.0 mg% and ranged during the next week from 11.0 to 12.3 mg.%

The patient remained well, without therapy, for about eight months but again was admitted to the hospital on October 24, 1973 because of a 4 cm mass in the subcutaneous area of the right flank, in the site of the previous incision. The metastatic x-ray survey was negative at this time. A repeat liver scan was interpreted as questionable for metastatic disease. Serum calcium on admission was 12.4 mg% and serum phosphate was 2.6 mg%. On October 25, 1973, the mass was excised and histologic examination showed a local recurrence of the same tumor. The serum calcium levels remained elevated postoperatively, ranging from 10.9 to 12.1 mg%.

Although the patient remained essentially asymptomatic in relation to her hypercalcemia, several radioimmunoassays for parathyroid hormone were performed during the next few months. An assay performed on October 29, 1973, using peripheral blood revealed a parathyroid hormone level of 180,[*] which was considered to be inappropriately elevated in relation to the serum calcium level. Selective venous sampling was carried out in December 1973 and revealed increased concentrations of parathyroid hormone in the superior vena cava and right innominate vein compared to other sites.

On February 20, 1974, the patient was admitted for the third time because of another recurrent mass in the right flank and also for an explorative operation of the neck for primary parathyroid disease. The serum calcium level at admission was 12.0 mg% and the serum phosphate was 2.6 mg%. On the following day, February 21, 1974, a parathyroid exploration was performed and a 1.6 gm parathyroid adenoma was removed from the left lower pole of the thyroid gland. In addition the nodule in the right flank, measuring 5 × 4 × 4 cm was excised. This again proved to be recurrent renal tumor. The patient has done well postoperatively and serum calcium levels have remained normal since the day after surgery, ranging from 8.7 to 9.9 mg%.

Comment

This patient also presented us with a difficult diagnostic problem. On the one hand, renal cell carcinomas are one of the two most common tumors known to produce hypercalcemia of malignancy. However, we were influenced by the fact that there was no response in the calcium level to nephrectomy, which at the time was felt to be a curative operation. At the second operation, with removal of the known metastatic lesion, there was again no response in the serum calcium levels. Finally, radioimmunoassayable parathyroid hormone was elevated in the peripheral blood and, of even greater importance, the highest concentration of parathyroid hormone appeared to be in the veins draining the neck region. We felt these findings justified exploration of the neck, even in a patient who was asymptomatic. Serum calcium levels of over 12 mg% are potentially dangerous and acute rises may lead to hypercalcemic crisis in such patients. In addition, we were concerned with protecting her remaining kidney from the development of nephrocalcinosis or nephrolithiasis, which could ultimately result in renal failure.

Discussion

It is well established that certain types of cancer can cause elevations in the levels of serum calcium (Table 1). There appear to be two mechanisms involved in the hypercalcemia: 1) destruction of bone by metastatic growth, and 2) production of a parathyroid hormone-like substance or Vitamin D-like sterol by the tumor itself. The most common cancer to produce hypercalcemia by bone destruction is cancer of the breast. This is not a rare phenomenon. Davis,[6] in his study encompassing 305 patients with cancer of the breast noted hypercalcemia in 22 patients or 7.2%. The incidence may even be higher, as suggested by Muggia,[14] who quoted a figure of 10–25% of patients with breast cancer. This can occur relatively abruptly in these patients, sometimes after the administration of hormonal therapy, either androgens, estrogens or both.[12] Multiple myeloma is also known to produce extensive bone destruction with an accompanying hypercalcemia. Hypercalcemia can be seen with other types of cancers in situations where bone metastases are present. This may also be the mechanism of hypercalcemia seen occasionally in lymphomas or leukemias, possibly due to wide-spread bone marrow involvement which may ultimately result in destructive skeletal lesions.

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[*] Normal in this laboratory up to 200 units.

Until recently there has been only indirect evidence of a clinical nature to suspect that cancers are able to produce a hormone-like substance. There are several criteria listed by Sherwood[21] that would suggest the presence of this substance in patients with cancers. These are: 1) absence of skeletal metastases; 2) low serum phosphate; 3) normal parathyroid glands at surgery or autopsy; 4) a fall in serum calcium levels after removal of the cancer; and 5) an increase of calcium levels with recurrence of the cancer. While not all of these criteria must be met, and there is actually some question as to the validity of some, a combination of several of these will strongly suggest the possibility that the cancer itself is responsible for the hypercalcemia.

Cancers of the lung and renal cell carcinomas are by far the most common tumors to produce this effect. These tumors represent at least 60% of the cases producing the syndrome of hypercalcemia of malignancy, as noted by Lafferty.[13] Bender[5] studied 200 patients with lung cancer in a prospective manner and found that 25 patients (12.5%) developed hypercalcemia at some stage of their disease. By cell type, 23% of patients with epidermoid carcinoma had elevated serum calcium levels, 12.7% of patients with large-cell anaplastic cancer, 2.5% of those with adenocarcinoma, and none of those with small cell cancers. Of these 25 patients, 14 had an absence of bone metastases, including 12 with epidermoid carcinoma and 2 with large-cell anaplastic cancer.

A group of 118 patients with renal cell carcinoma were studied by Warren.[23] Of these 15 (13%) had elevated calcium levels before the operation. General summaries of the types of cancers causing hypercalcemia of malignancy have been published in the last ten years by Goldberg,[9] Lafferty,[13] Omenn,[15] and Ariyan.[2] It has been noted by several authors that squamous cell cancers are often responsible for hypercalcemia, including head and neck tumors. A group of nine patients with these tumors and hypercalcemia were recently described by Ariyan[2] and another group of 5 patients was reported by Terz.[22] Other squamous cell carcinomas that have, on occasion, produced hypercalcemia of malignancy include cancers of the bladder, cervix, esophagus, vulva, and penis. There are, in addition, individual case reports of patients with other cancers which have produced the clinical picture of hypercalcemia of malignancy (Table 1).

Considerable efforts have been expended during the past 10 years to isolate a parathyroid hormone-like substance produced by these cancers. The development of the technique for measurement of parathyroid hormones by radioimmunoassay has helped; but the overall picture is still somewhat confused. It appears at this point that the parathyroid hormone circulating in patients with primary hyperparathyroidism is immunoheterogenous. Arnaud[4] believes there is evidence of at least three circulating forms of immunoreactive parathyroid hormones in patients with primary hyperparathyroid disease. He was able to measure serum parathyroid hormone levels in patients with hypercalcemia of malignancy, but these levels were lower than those found in patients with primary hyperparathyroidism. He felt this might be due to an alteration in the ratio of immunoreactive forms of circulating parathyroid hormones in the two conditions.[3] In contrast, Powell and associates[18] were completely unable to detect parathyroid hormones in the blood or tumor tissues of patients with hypercalcemia of

TABLE 1. *Cancers Causing Hypercalcemia*

A. Caused by metastatic destruction of bone

    Breast cancer—most common
    Multiple myeloma
    Lymphoma and leukemia (?)

B. Caused by parathyroid hormone-like substances
  1. Most common

    Lung cancer—especially epidermoid
    Renal cell carcinoma

  2. Less common

    Head and neck cancer
    Ovarian cancer
    Hepatoma
    Pancreatic cancer
    Bladder cancer
    Endometrial cancer
    Lymphomas

  3. Isolated case reports

    Esophageal cancer
    Colon cancer
    Rectal cancer
    Cervical cancer
    Vulvar cancer
    Uterine Leiomyosarcoma
    Cancer of the penis
    Prostatic cancer
    Adrenal cancer
    Melanoma
    Hemagiopericytoma
    Branchial rest cancer
    Parotid cancer
    Breast cancer
    Mammary dysplasia

malignancy, but they were able to show that extracts of these tumor tissues caused active calcium resorption from bone in vitro. Again, in contrast, Sherwood[21] was able to detect measurable levels of parathyroid hormone in 7 patients but not in an additional 6 hypercalcemic patients with cancer. Measurable levels in the 7 patients were below those of patients with parathyroid adenomas. He felt that a low concentration of hormone was produced by the tumors, but that the generally large size of the cancers would compensate for the low concentration.

Most investigators in this field have felt that the mechanism of calcium elevation is not a simple one. Roof[20] felt that hypercalcemia of malignancy may be associated with two or more types of parathyroid hormones. These include one which cannot be distinguished from normal parathyroid hormone, one which differs immunologically from normal parathyroid hormone, and possibly a third hormone with a higher ratio of immunologic to calcium-increasing activity. Riggs and associates[19] felt that either the parathyroid hormone of hypercalcemia of malignancy may be different from the parathyroid hormone of primary hyperparathyroidism, or more likely, that the immunoreactive material in the serum of patients with hypercalcemia of malignancy is a precursor or an intermediate form of the normally secreted hormone. Powell and associates[1] have suggested the possibility that a humoral substance other than parathyroid hormone, perhaps a Vitamin D-like sterol, may be responsible for the hypercalcemia of malignancy. Obviously, there appears to be more investigative work necessary for complete understanding of the involved mechanisms. Throughout the country, there are considerable differences in laboratories as to the ability to detect measurable hormone levels in patients with hypercalcemia of malignancy. If one uses the services of one of these laboratories, one, therefore, must know the capabilities of the individual laboratory in interpreting the results. Riggs and associates[19] have perhaps been the most successful in distinguishing between hypercalcemia of malignancy and primary hyperparathyroidism, and have been able to diagnose 16 of 18 patients with the former condition by radioimmunoassay.

As pointed out earlier, the establishment of the differential diagnosis between primary hyperparathyroidism and hypercalcemia of malignancy is important clinically, and the problem is not at all rare. Farr and associates[8] at Memorial Hospital have recently written about 100 patients with cancer and primary hyperparathyroidism; of these, 29 patients had active cancer at the same time as primary parathyroid disease. As one becomes more aware of the possibility of hypercalcemia causing moderate and severe symptoms in patients with cancer, undoubtedly more patients with this syndrome will be discovered. Although we would expect that a more highly refined form of radioimmunoassay would ultimately permit differentiation between the two conditions, these tests are still in a developmental stage, and one has to rely on other means of making a definitive diagnosis.

Lafferty[13] suggested that certain aspects of the patient's history and certain laboratory tests might be helpful in differentiating between primary hyperparathyroidism and hypercalcemia of malignancy. He observed that the hypercalcemia was of more rapid onset in malignancy than in the primary parathyroid disease. He also noted that renal disease and osteitis fibrosa cystica were more common in patients with primary parathyroid disease. However, none of these are absolutes and they probably have value in only a limited number of patients. Lafferty[13] also noted that the serum calcium levels were more frequently above 14 mg% in patients with hypercalcemia of malignancy, that anemia was more common in these patients, that the serum chloride levels were lower, and that these patients responded to the administration of adrenal steroids to a greater extent than patients with primary hyperparathyroidism. Again, exceptions to these criteria are so frequent that we have felt that they have only limited usefulness. Lafferty[13] admitted that such tests as serum phosphate, serum uric acid levels, tubular reabsorption of phosphorus, and calcium infusion tests had little or no value in differentiating between the two conditions. Others have pointed out that the serum phosphate levels are commonly high in patients with hypercalcemia due to metastatic bone destruction, whereas low normal levels or low levels of phosphate are seen in patients with primary hyperparathyroidism and parathyroid hormone-secreting malignancies.

In establishing a practical modus operandum for making a differential diagnosis in patients with cancer and hypercalcemia we have found the following points to be more useful than the criteria of Lafferty:[13]

1) A history of hypercalcemia prior to the development of the malignancy. With the extensive use of the SMA-12 there are many records of patients with prior serum calcium determinations. In some patients, slight or inconsistent elevations of serum calcium may have been overlooked. This is somewhat similar to the situation of a patient with a pulmonary lesion, where one can compare the findings on present chest x-ray films with those films taken in the past. The presence of one or two slightly elevated serum calcium levels, which might not have been further investigated, may render the diagnosis of hypercalcemia of malignancy less likely.

2) The type of cancer itself is of considerable importance in making the differential diagnosis. If the patient had, for example, a carcinoma of the stomach, the possibility of hypercalcemia of malignancy would be less likely since this cancer has not yet been described as one of those producing this syndrome. If, on the other hand, one is dealing with a patient with a renal cell carcinoma, hypercalcemia of malignancy is more likely, although, as in the case of our third patient, this does not rule out the possibility of a primary hyperparathyroidism. In working with these

patients one should be aware of the types of cancer which are most commonly associated with hypercalcemia of malignancy.

3) The effect of surgery or other types of treatment on the elevated serum calcium levels is of great importance. If the cancer, either the primary or recurrent tumor, is treated adequately, the elevated serum calcium levels should fall significantly in most patients with hypercalcemia of malignancy. This is not an absolute, as noted by Warren[23] in some of his patients with renal cell carcinomas. However, if there is a positive response, one can conclude that hypercalcemia of malignancy was present. If there is no significant or long-lasting response, there is the possibility that either significant metastatic disease is present, which should lead to further investigation, or the patient may have primary hyperparathyroidism.

4) If a diagnosis cannot be made definitively on the basis of the above criteria, specific testing for primary hyperparathyroidism should be performed. As noted recently by Ackerman and Winer,[1] most of the standard tests for localizing primary parathyroid disease have been generally unsuccessful. However, selective venous sampling with radioimmunoassays performed on blood from the large veins of the neck and mediastinum appears to have had a relatively high rate of success recently, as noted by Powell.[17] In these studies, blood from the internal jugular vein, innominate veins, and superior vena cava were obtained and tested. This test may even be more accurate if carried out in combination with superior and inferior thyroid arteriography and venography, and venous sampling of the thyroid veins themselves, as noted by Doppman.[7] These tests require the assistance of an individual skillful in selective angiography and a laboratory equipped to do radioimmunoassay for parathyroid hormone. However, the tests can be extremely helpful in situations where the definitive diagnosis is still ambiguous, as in our third case.

There is one additional situation that is, fortunately, probably quite rare. This is in the patient who has hypercalcemia due to both primary hyperparathyroidism and malignancy occurring simultaneously. A probable situation of this type occurred in the patient described by Hodgkinson,[10] where a parathyroid adenoma was excised and the calcium levels remained elevated. The patient died a month later with a carcinoma of the renal pelvis. It is fortunate that the co-existence of these two syndromes is rare, since merely differentiating between them is itself highly challenging.

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The Precision of a Special Purpose Analog Computer in Clinical Cardiac Output Determination

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Three hundred dye-dilution curves taken during our first year of clinical experience with the Waters CO-4 cardiac output computer were analyzed to estimate the errors involved in its use. Provided that calibration is accurate and 5.0 mg of dye are injected for each curve, then the percentage standard deviation of measurement using this computer is about 8.7%. Included in this are the errors inherent in the computer, errors due to baseline drift, errors in the injection of dye and actual variation of cardiac output over a series of successive determinations. The size of this error is comparable to that involved in manual calculation. The mean value of five successive curves will be within 10% of the real value in 99 cases out of 100. Advances in methodology and equipment are discussed which make calibration simpler and more accurate, and which should also improve the quality of computer determination. A list of suggestions is given to minimize the error involved in the clinical use of this equipment.

THE ESTIMATION of cardiac output has become a frequent and necessary procedure in clinical diagnosis and patient monitoring. Of the various methods of measuring cardiac output, dye-dilution studies are readily performed, and perhaps offer the most accurate estimate.[2] However, manual calculation of the area under the curve remains a time consuming and laborious task, although a number of simplified procedures have been devised.[4,7,18] The development of special purpose analog computers has enabled the clinician to accomplish bedside monitoring of cardiac output with an instantaneous determination of its value. However, the ability of these computers to integrate the area under a dye-dilution curve accurately has recently been questioned.[3] In this report we compare the results of the computer and manual methods of cardiac output determination to analyze the errors in both methods using a variety of statistical approaches.

Technical Methods

Three hundred cardiac output determinations were made on 25 adult patients prior to and for 24 hours following vascular surgery using the dye-dilution technique with indocyanine green as the indicator. For this purpose, we inserted an Intramedic polyethylene catheter percutaneously into an antecubital vein and passed it into the right atrium. A Longdwel catheter was inserted into a radial artery. Indocyanine green, usually 2.5 or 5.0 mg, was injected by the slug method via the venous catheter and arterial blood was withdrawn at 19.3 ml/minute through the cuvette of a Gilson GME Dye Tracer by a Harvard Infusion-Withdrawal Pump. The DC output of the densitometer was connected to the input of a Water CO-4 Cardiac Output Computer. Dye-dilution curves were also inscribed on an Electronics for Medicine oscillographic recorder. Since the densitometer-cuvette response was linear with a zero intercept,[15] a single point calibration at 10 mg/L of blood set at about 100 mm of paper was made with each new vial of dye. Determination of the area under the curve, and thus of the value for the cardiac output, was performed in two ways: computer and manual calculation. The computer calculated by integrating the area from the initial upward deflection to a point on the descending slope that corresponded to 75% peak deflection. Then, by assuming exponential decay it predicted the area under the remainder

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of the primary curve from the computed area between 75% and 50% peak height. Manual calculation, using half second intervals, was accomplished by a modification of the Stewart-Hamilton method similar to that reported by Hoffman.[9]

For statistical analysis, the 300 curves could be separated into 74 sets of multiple determinations. Each set was comprised of 2–8 curves taken on a patient within 20 minutes.

Statistical Methods

Most previous studies of this nature[1,3,6,8,13,17] have reported the mean and standard deviation of the percentage differences between the values obtained by the computer and manual calculation. In these comparisons there is the implication that the manual method was "perfect" and that all error was due to the computer. However, both methods have inherent errors. Thus, the value we obtain for the cardiac output via either method should be considered as the sum of the true cardiac output and an error term which depends upon the method being used. We have previously outlined the required statistical procedures to be followed to make a valid comparison of measurement methods.[12] Necessarily, the differences in the properties of the error terms for the two methods rather than the difference between the values obtained in the two ways must be considered. From our sample of measurements, we were able to arrive at estimates of these properties. Since our data indicated that the magnitude of the error terms for both methods was not independent of the magnitude of cardiac output, we made a log transformation of the data. This resulted in the error terms becoming independent of the value and allowed us to proceed with the statistical analysis.

In comparing the properties of the error terms for the two methods, we first considered their accuracy: that is, whether or not the error terms tend to introduce bias into the experimental values. By using a paired t-test we tested for a significant difference between the two methods in this regard.

Then, we compared the precision of the methods, or the variability of the percentage error terms. The more precise the method, the smaller the standard deviation of the percentage error term, and consequently the fewer the number of determinations required to obtain a good estimate of the true cardiac output. For each of the two methods, this was accomplished by subtracting the overall estimate of the variance in the error terms derived by the method described by Thompson[16] from the pooled estimate of the variance of the error terms based upon the 74 sets of multiple determinations. Both estimates included the error due to computation; however, the latter also included the actual variation from curve-to-curve in cardiac output in a patient in a stable state, variation in dye injection, and other factors affecting the curves themselves but independent of the method of calculation. This difference therefore, was an estimate of the variance of the curve-to-curve variation alone. This was done for both manual and computer values, the average of which is a more refined estimate of the variance of the curve-to-curve variation. This difference was then added to the variance based on Thompson and the square root taken to obtain a clinically relevant estimate of the overall standard deviation of the percentage error for each of the four subsets of data. These four subsets were: manual, 2.5 mg and 5.0 mg injections; and computer, 2.5 mg and 5.0 mg injections.

From these data, using standard statistical formulas,[14] we then were able to determine how many curves should be run on a patient to obtain an estimate of his cardiac output with a desired level of confidence.

Results

Figure 1 shows the computer determined values plotted against the manually calculated values for all 300 curves. Basic statistics for these data are presented in Table 1. The average percentage difference and the standard deviation of the percentage difference between the two methods are included mainly for comparison with previous reports. A graph of absolute value of the percentage difference between the two methods vs. the manually determined cardiac output (Fig. 2) shows that the size of the percentage difference seems not to depend upon the magnitude of cardiac output; the correlation coefficient for these points is −0.01. This is more consistent with an assumption of the standard deviation of the absolute error term being proportional to cardiac output, rather than such standard deviation being constant over the range of cardiac outputs.

Differences in Accuracy

The small average value of percentage differences between the two methods (Table 1) is an indication of little, if any, difference between the two methods in this regard. A paired t-test, a more sensitive method of distinguishing such a difference, indicated that the mean difference between the two methods was not significantly different from zero ($t = -0.585$, 299 df, $p > 0.50$). Thus, we have no indication from our data of a difference in bias between the two methods, and they can be considered equally accurate in our restricted use of the term.

Estimates of Relative Precision from Multiple Determinations

In Fig. 3 are the graphs of the standard deviation of each set of multiple determinations vs. the mean cardiac output of the set, for both manual and computer values. Although there is a great deal of scatter, there is a significant regression of standard deviation on the magnitude of cardiac output for each method. Again, this supports an assumption of standard deviation of absolute error terms proportional to cardiac output rather than independent of cardiac output.

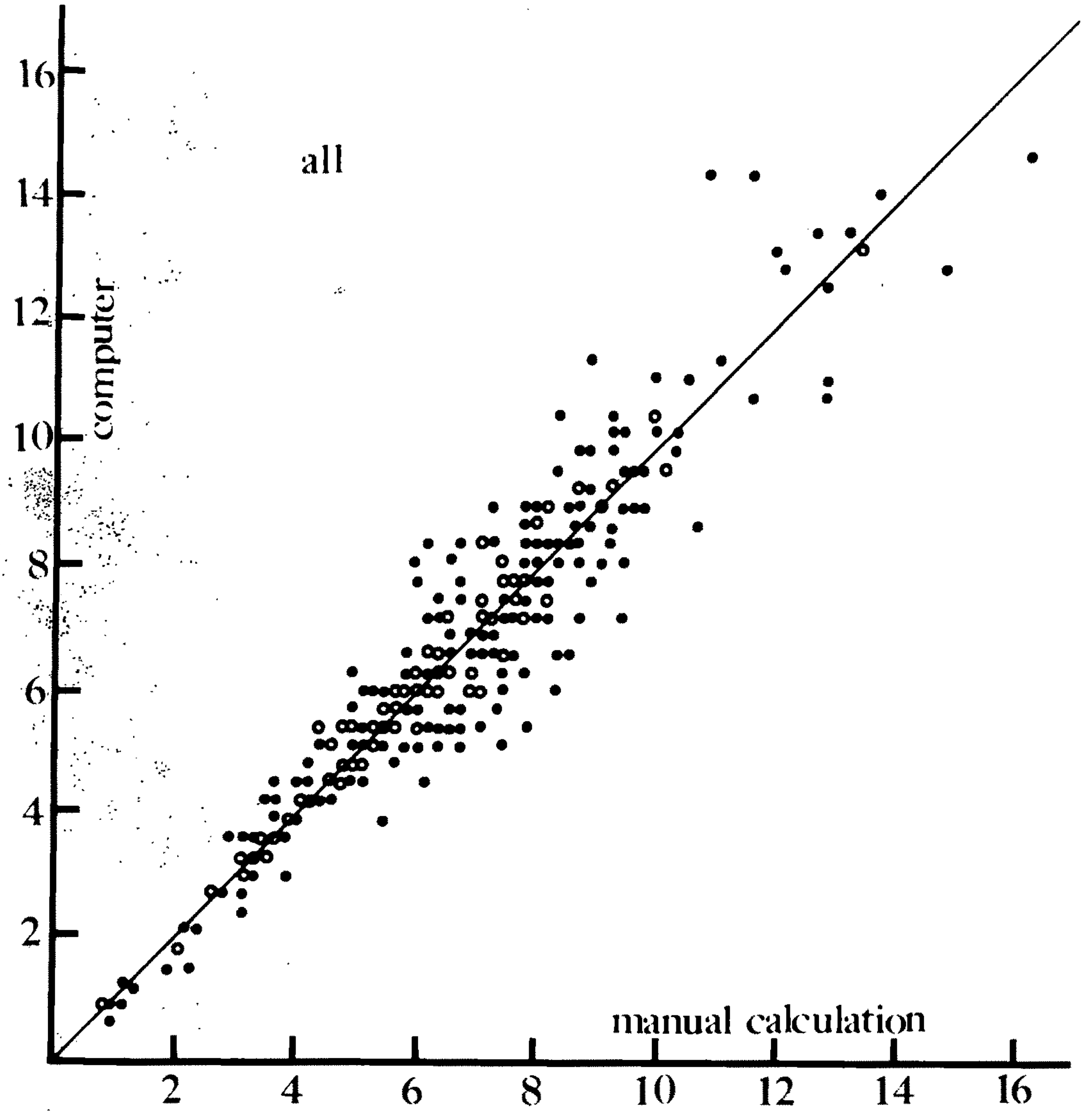

FIG. 1. Graph of computer values vs. manual values of cardiac output (l/min) for 300 curves. Line of identity is shown. Open circles indicate 2 or more approximately coincident points.

The pooled estimates for the error terms for each method, from the relative standard deviations of all 74 sets are: manual, 0.086 (or 8.6%); computer, 0.110 (or 11.0%).

Estimates of Relative Precision by the Method of Thompson

Using our adaptation of this method, we arrived at an estimate of the standard deviation of the percentage errors in the two methods for 5.0 mg curves, exclusive of curve-to-curve variation. These estimates are: manual method, 8.0%; computer method, 6.8%. Estimates based on all 300 curves and the 2.5 mg curves are erroneous because some curves did not obey the requirements of the computed (see Discussion). If we consider only the 288 curves with indicated cardiac output greater than 2.5 l/min, we obtain the

TABLE I. *Summary of Statistics on Dye-Dilution Curves*

	All Curves		2.5 Mg Inj.		5.0 Mg Inj.	
	Computer	Manual	Computer	Manual	Computer	Manual
Minimum C.O., l/min	0.70	0.84	0.07	0.84	2.56	2.54
Maximum C.O., l/min	14.74	16.20	14.40	12.84	14.74	16.20
Mean C.O., l/min	6.61	6.63	6.05	6.11	7.10	7.09
SD of C.O., l/min	2.65	2.58	2.53	2.41	2.63	2.62
Number	300*		129		168	
Corr. Coeff.	0.95		0.94		0.96	
Avg PCTD†	−0.37%		−1.42%		+0.69%	
SD of PCTD†	11.75%		12.86%		10.59%	

* In three cases, 1.25 mg was injected.

† Average and standard deviation of the percentage difference between the two methods of calculation for each curve.

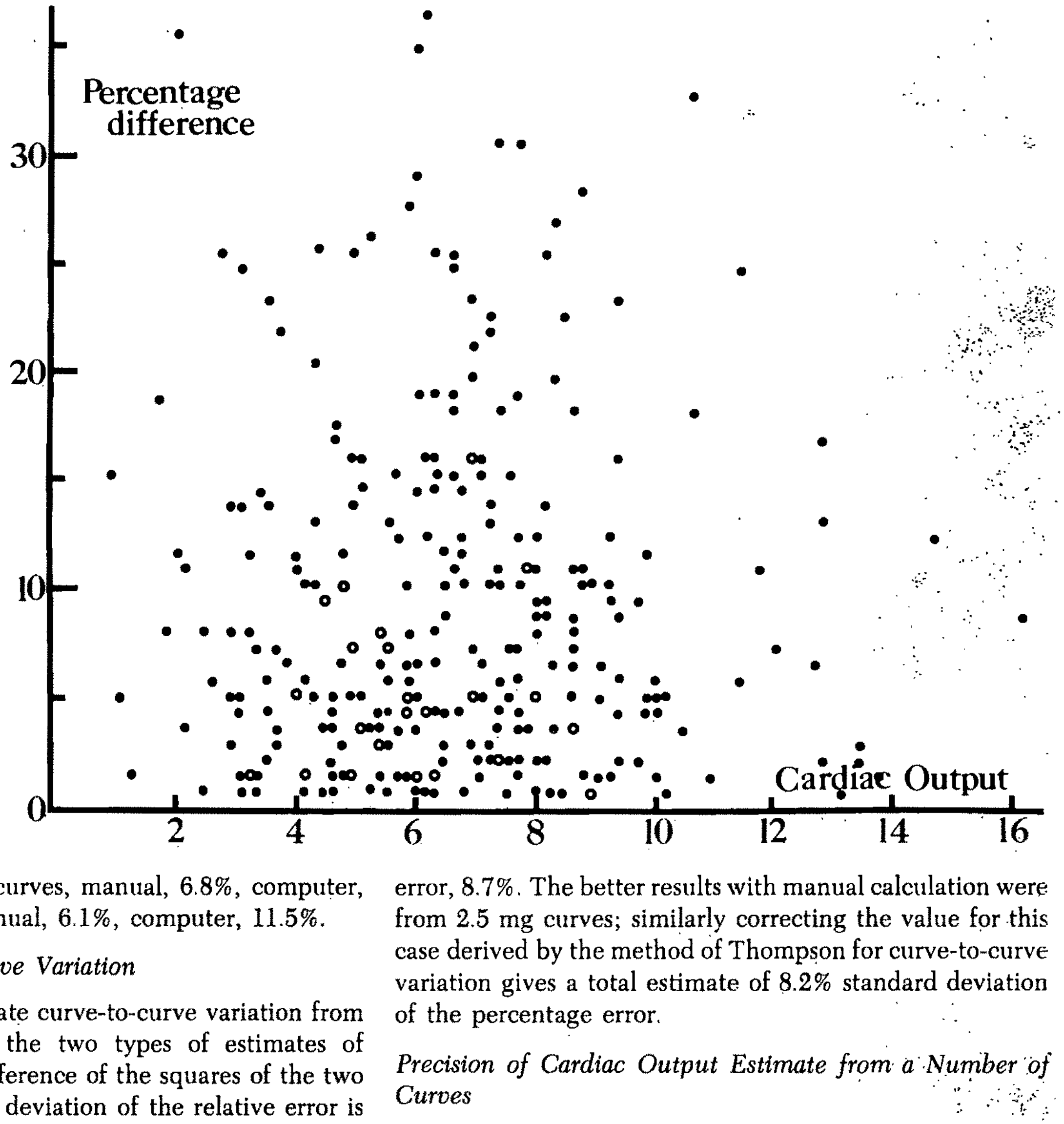

FIG. 2. Graph of absolute value of percentage difference (100 × (computer values − manual value) / manual value) vs. manually determined cardiac output (l/min) for 300 curves. Open circles indicate 2 or more approximately coincident points. Correlation coefficient is −0.01.

following estimates: 288 curves, manual, 6.8%, computer, 9.4%, 2.5 mg curves, manual, 6.1%, computer, 11.5%.

Estimate of Curve-to-Curve Variation

We proceeded to estimate curve-to-curve variation from the differences between the two types of estimates of relative precision. The difference of the squares of the two estimates of the standard deviation of the relative error is .0027 for manual values, and is .0033 for computer values. The mean of these two estimates is .0030. The square root of this value is an estimate of the standard deviation of the relative error term due to curve-to-curve variation, and is 0.055, or in terms of the percentage error, 5.5%.

Of the four subsets of data, the 5.0 mg injections demonstrated a possible superiority to 2.5 mg injections when the computer is used. The likely overall standard deviation of the relative error using 5.0 mg injections, including curve-to-curve variation was calculated by adding the squares of the individual standard deviations to arrive at the square of the overall standard deviation. In this case $(0.055)^2 + (0.068)^2 = 0.0076$, gave a resultant standard deviation of the relative error of 0.087, or of the percentage error, 8.7%. The better results with manual calculation were from 2.5 mg curves; similarly correcting the value for this case derived by the method of Thompson for curve-to-curve variation gives a total estimate of 8.2% standard deviation of the percentage error.

Precision of Cardiac Output Estimate from a Number of Curves

Using standard statistical equations, the mean value of five curves taken on a patient in a stable state, using 5.0 mg injections and calculating by computer, will be no more than 7.8% from the true value of cardiac output in 95 cases out of 100, and no more than 10.0% away in 99 cases out of 100, barring systematic error. Use of the manual method on 2.5 mg curves will only give a slightly more precise estimate (95% limits: ± 7.3%; 99% limits: ± 9.4%).

Discussion

The results of this study clearly support the use of this special purpose analog computer in the determination of cardiac output using the dye-dilution technique. The mean value of five determinations, using the computer with 5.0

mg injections, will give a reasonably precise estimate of cardiac output, provided calibration is done properly. The computer is less precise when 2.5 mg injections are used, but the cost of extra dye needed for precise computer estimation is more than outweighed by the saving in time the computer affords to the clinician.

The reason for eliminating values less than 2.5 l/min from the statistical consideration was that they were taken on patients who had myocardial decompensation. Curves taken on such patients cannot fulfill the assumptions made in the use of the CO-4 computer, namely that the decay of the curve be exponential from 75% to 50% of the peak. It should be noted that studies with similar computers used to determine cardiac outputs in dogs have generally shown good accuracy at flow rates below 2.5 l/min.[17] Thus, at low flow rates in the adult human the inaccuracy is probably more due to improper application of the technique rather than to inherent error in the computer itself. The curves reported by Malooly *et al.*[11] would be calculated as lower than normal cardiac outputs because of the magnitude of left-to-right and right-to-left intracardiac shunts although the true value would be greater than normal. In these cases the dye-dilution curves can be useful in the diagnosis of shunting.

To minimize errors involved in the use of the dye-dilution technique either with manual or computer calculation of cardiac output, we must consider the sources of error in the technique itself and in the two methods of computation. Errors that affect the accuracy and precision of the technique itself include: inaccurate mixing of powdered dye in diluent, inaccurate dilution of dye in blood for calibration, and inaccurate measurement of the injected amount of dye. Such errors in calibration can be minimized by using the electronic calibration method we have described elsewhere.[15] This is essentially a one-time accurate calibration with dye-in-blood, using the output of the densitometer as monitored by the computer for subsequent calibration. This gives more consistent results than repeating a dye-in-blood calibration each time the equipment is used.

An error can also be caused by the nonlinearity of the cuvette-densitometer system in its response to standard concentration of dye. In order to use the single point calibration suggested in this paper, the calibration curve should be linear and have a zero intercept. Previously, we documented this to be true for the system we have used.[16] As demonstrated by Cropp[5] not all systems behave in this fashion. Although this nonlinearity will not interfere with the precision of the calculating techniques, it may lead to a significant inaccurancy of the value of the cardiac output. However, it is believed that the deviation from linearity does not introduce major errors, in accuracy[5] probably because it occurs at very low dye concentrations.

The manual method of calculation is subject to the following major errors: measuring the height of the curve at frequent intervals, the use of an approximation formula required to determine area from these values, and fitting the downslope of the curve to a straight line on semilogarithmic paper.[10] Improvement in the error due to this method would mainly be obtained by measuring the height of the curve at more frequent time intervals, and by using a more complicated approximation formula. This would ob-

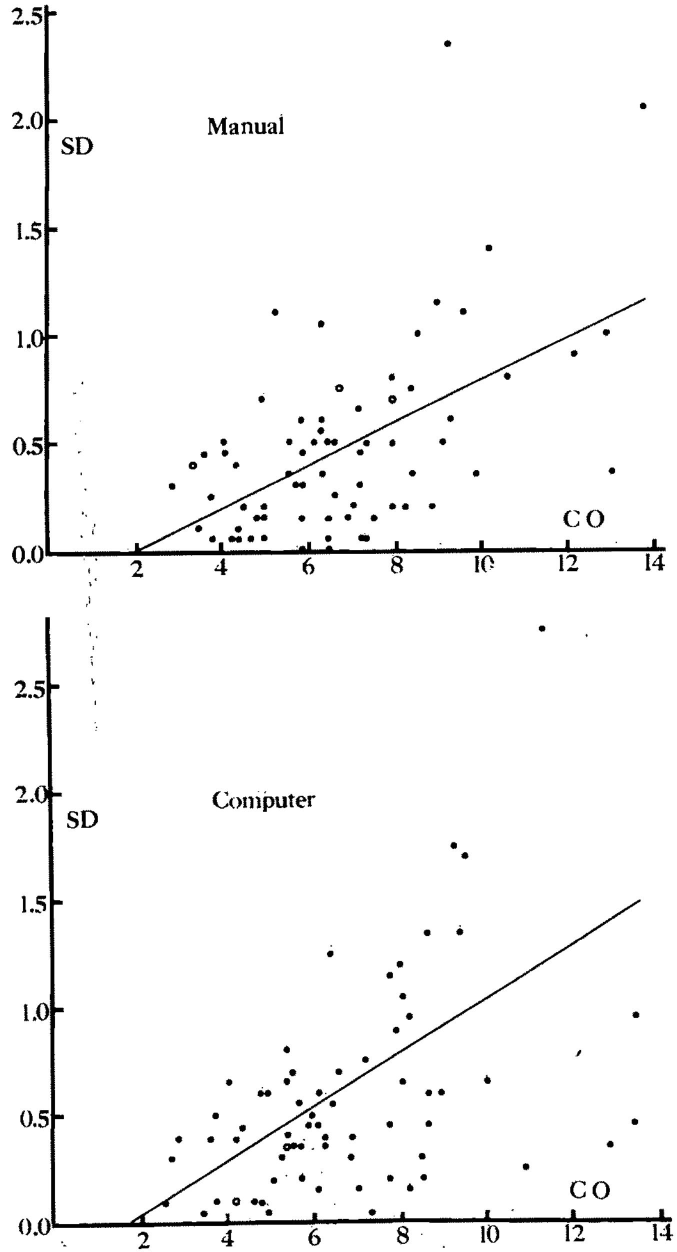

FIG. 3. Graphs of standard deviation (l/min) of each of the 74 multiple determinations vs. the mean cardiac output (l/min) of each of the 74 multiple determinations for the manual and computer values. The equations for the indicated linear regression lines are: manual, $SD = -0.186 + (0.098\ CO)$; computer, $SD = -0.213 + (0.114\ CO)$. Both the slopes are significantly different from zero ($p < 0.001$); the intercepts are not ($p > 0.50$).

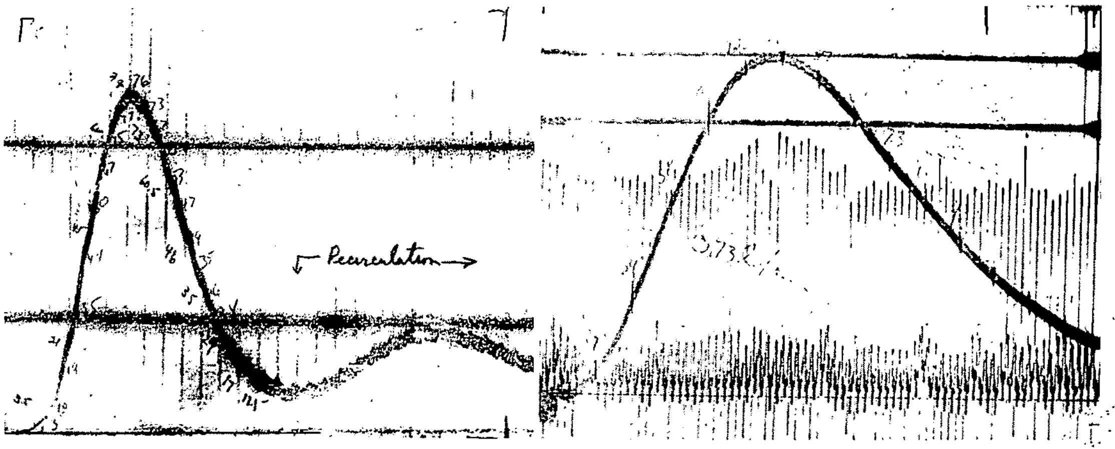

FIG. 4. Dye-dilution curves of normal (left) and low (right) cardiac outputs. In the normal curve the descending slope of the curve is semi-logrithmic throughout and recirculation appears as a second curve. In the abnormal curve, the descending slope does not decay semi-logrithmically.

viously and more time to that required for manual calculation.

Major sources of error in the computer method include: inaccurate calibration of the computer, baseline drift which may occur during appearance time, and the pulsation often seen in clinical dye-dilution curves. In our laboratory, calculations based on representative curves have indicated that a pulsation of ± 5% of peak height could possibly cause an error of ± 10% in the computer's determination, due to incorrect signally of the 75% and 50% points on the downslope of the curve (unpublished results). From the present data we cannot say whether so large an error occurs in practice due to this phenomenon. However, improvements in computer performance are afforded by refinements in equipment now available. For example, both the Waters XP-302 Densitometer and the Lyons dye-dilution system now have a switch to allow smoothing of the pulsation artifact. The Lyons system and the newest Waters densitometer also have an automatic baseline-setting switch which is much easier to use than the knob required to set the baseline on most other equipment. This should help to minimize the error due to baseline drift.

Objections to the use of dye-dilution to estimate the cardiac output often include the time necessary to calibrate the equipment, problems in setting the baseline, and the amount of time necessary to calculate the curves by hand, or the allegedly enormous error in the use of speical purpose analog computers such as the CO-4[3]. However, use of the electronic calibration method reduces calibration time for each clinical use to the two minutes or so necessary to check the calibration of the computer,[15] and this report shows that the overall error involved in the use of the CO-4 computer, including baseline drift as we experienced it in our first year of clinical use, is about the same as the error in the manual method but with results instantly available.

To insure that the above estimate of error is equalled or bettered in the monitoring of cardiac output with an analog computer, we make the following suggestions based upon previous studies, the present data, and our own clinical experience:

1. Inject dye at or as close as possible to the right atrium.

2. Use the electronic calibration method we have described elsewhere[15] with a digital-display computer that can also be used to monitor the output from the cuvette-densitometer. If this monitor has a gain adjustment, keep it set as a constant value.

3. Choose an input which will enable precise calibration of the integrating circuitry fo the computer. For example, an electronic signal equivalent to 5 mg/l for thirty seconds with the computer set for a 5.0 mg injection should indicate a cardiac output of 2.00 l/min which can be adjusted to within ± 0.01, or 0.5%.

4. Mix the dye accurately, and whenever possible use 5.0 mg injections, taking special care that syringes and catheters are properly filled.

5. After dye is injected, adjust for any baseline drift for a few seconds before putting the computer into the "compute" mode, if such switching is done by hand. This should minimize error due to baseline drift. Once an appearance time has been found, such baseline adjustment can easily be continued until just before the curve appears. If the baseline still shifts after the last adjustment, a downward drift means that the computer's value is too high; an upward drift, too low.

6. Critically analyze any curves taken on patient with known or suspected cardiac or pulmonary shunts. If they show signs of non-uniform or non-exponential decay, then the computer's value cannot be accurate. (Figure 4) In fact, even a manually calculated value from such a curve may not indicate the real cardiac output.[11]

7. If the computed cardiac output is grossly different from that estimated on the basis of clinical impressions, ascertain that all settings on the equipment are correct before taking any action on the basis of the computed car-

diac output. For instance, setting the computer to the wrong value for the amount of dye injected introduces a proportional error into the value of the cardiac output.

If the above precautions are taken, then an accurate estimation of the cardiac output can be obtained within minutes of catheter placement.

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Improvement in Lower Esophageal Sphincter Pressure Following Surgery for Complicated Gastroesophageal Reflux

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A comparison was made of the pre- and postoperative lower esophageal sphincter (LES) pressures in nine patients undergoing a posterior gastropexy for complicated gastroesophageal reflux. LES pressure was increased from 4.4 ± 0.4 mm Hg to 13.9 ± 0.5 mm Hg following surgery ($p < .01$). The ratio of the change in LES pressure compared to the change in gastric pressure during increases in intra-abdominal pressure $\Delta S/\Delta G$, was 0.59 ± 0.05 preoperatively and 0.94 ± .01 postoperatively ($p < .01$). All patients were asymptomatic after surgery. Both the resting LES pressure and the $\Delta S/\Delta G$ ratio following surgery were significantly less than the comparable values obtained in an age-matched control population ($p < .01$). These studies suggest that the clinical improvement following surgery for gastroesophageal reflux may be due to the increase in resting LES pressure and the improved response of the LES to increased intra-abdominal pressure.

IT HAS BEEN SUGGESTED recently that the primary factor in the prevention of gastroesophageal reflux is the competence of the physiologic lower esophageal sphincter (LES).[2,12] The presence of a hiatus hernia is now considered to be less important in the pathogenesis of gastroesophageal reflux.[2,4,5,12] With this new emphasis on LES competence, the surgical approach to treating gastroesophageal reflux has shifted from the simple repair of a hiatus hernia to more detailed approaches to improve LES competence. These surgical approaches have received enthusiastic support based on clinical patient evaluations. While acknowledging that the majority of patients are improved after the effective use of a Nissen, Belsey or Hill type of surgical procedure, the mechanism by which these operations improve gastroesophageal competence is not clear.[1,9,14] An improvement in LES strength has been suggested.[3,7] The purpose of this study is to compare the LES resting pressure and the changes in LES pressure with increase in intra-abdominal pressure in controls and in patients with symptomatic gastroesophageal reflux studied both before and after surgery.

Methods

The study group consisted of nine patients with decreased LES pressure and symptoms of recurrent heartburn aggravated by postural change. Each patient was either a failure of medical management or suffered a complication of gastroesophageal reflux. The patients and their indications for surgery are listed in Table 1. A hiatus hernia was present in four of the patients. All patients underwent esophageal manometric study before, and a mean of 3.7 weeks after, surgery. Each patient had a cine-esophogram and esophagoscopy prior to surgery. Ten age-matched controls with no gastrointestinal symptoms were also evaluated. The controls consisted of 5 males and 5 females, aged 25–70 (mean, 45).

Water-filled polyvinyl catheters, 1.4 mm internal diameter, were used to transmit intra-luminal pressures to external transducers (Statham). The output from each transducer was recorded on a Beckman curvilinear ink-writing recorder. Three recording catheters were arranged to form a single assembly with three side orifices, 1.2 mm diameter, at 5 cm intervals. The pressure recording tubes were infused

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TABLE 1.

Patient	Age and Sex	Hiatal Hernia	Indication for Surgery
A.O.	18 y M		Intractibility*
M.B.	25 y M		Intractibility*
S.M.	33 y F	++	Stricture
R.N.	37 y F		Intractibility
J.P.	37 y M	++	Esophageal bleeding†
R.M.	41 y F		Intractibility*
E.S.	58 y F	++	Intractibility*
A.D.	62 y M	++	Esophageal bleeding†
F.M.	67 y M		Stricture

Mean Age = 42.0 years

* Erosive esophagitis by esophagoscopy.

† Upper gastrointestinal hemorrhage with source of bleeding from esophagitis as diagnosed by esophagoscopy.

with distilled water, by a syringe pump, at a constant rate of 1.2 ml per min. All pressures were expressed using gastric pressure as a zero reference. The manometric records were tabulated using the midrespiratory pressure recorded from the segment of the LES manifesting the maximal pressure.

Manometric studies were performed with the patient resting quietly in the supine position, after an 8 hr fasting period. Belt pneumographs around the chest and over the larynx were used to monitor respiration and swallowing, respectively. The recording assembly was positioned with all orifices in the stomach. Following a 20 min rest period, the assembly was moved, at 1 cm intervals, through the full length of the esophagus. Following this diagnostic evaluation, the recording assembly was positioned and anchored so that pressures were simultaneously recorded from esophagus, LES and stomach. Intra-abdominal pressure was increased by simultaneous raising of both extended legs. Results of these maneuvers were expressed as change in pressure and represented the differences between simultaneously obtained increased gastric, LES and esophageal pressures. Thus, a ratio for the increase in LES pressure ΔS to an increase in gastric pressure ΔG was determined $\Delta S/\Delta G$. If gastroesophageal reflux occurred (sudden equalization of gastric, LES and esophageal pressures indicating continuity of stomach and esophagus). these values were not tabulated.

Operative Technique

The operation, illustrated in Fig. 1, was a posterior gastropexy,[6] modified by placing two sutures above the level of the gastroesophageal junction so that a very short segment of the terminal esophagus was placed in an intragastric position. The gastroesophageal junction was cleared off on the lesser curvature side. Four sutures were placed through the anterior and posterior seromuscular layers of the stomach, two above and two below the gastroesophageal junction. The upper two sutures were also passed through the muscle fibers of the esophagus. The sutures in the seromuscular portion of the stomach were placed very close to the lesser curvature side so that the main effect of this placement was to give strength to the sutures, as well as to give a very short segment of intragastric esophagus. All of the sutures were passed through the median arcuate ligament. When the sutures were tied down, the muscular sling at the gastroesophageal junction was demonstrably tightened, a short length of terminal esophagus was placed intra-gastrically and the gastroesophageal junction was firmly anchored within the abdomen. To prevent too tight a closure around the esophagus, a #18 plus a #30 red rubber tube (not illustrated) were placed through the esophageal junction prior to tying down the sutures.

Results

Figure 2 shows the resting LES pressures in controls and in all patients studied before and after surgery. The mean LES pressure prior to surgery, 4.4 ± 0.4 mm Hg, increased to 13.9 ± 0.5 mm Hg following surgery ($p < .01$). The age-matched control population had an LES pressure of 18.7 ± 1.8 mm Hg. The LES pressure in the controls was significantly greater than both the pre- and postoperative pressures in the patient group ($p < .01$).

Figure 3 shows the ratios of the change in LES pressure (ΔS) to the change in intra-abdominal or gastric pressure (ΔG). In the controls, the ratio was 1.84 ± 0.12 compared to a ratio of 0.59 ± 0.05 in the patients prior to surgery ($p < .01$). Following surgery, the $\Delta S/\Delta G$ ratio was increased to 0.94 ± .01. This change was statistically significant, $p < .01$, but remained less than that obtained in controls, $p < .01$.

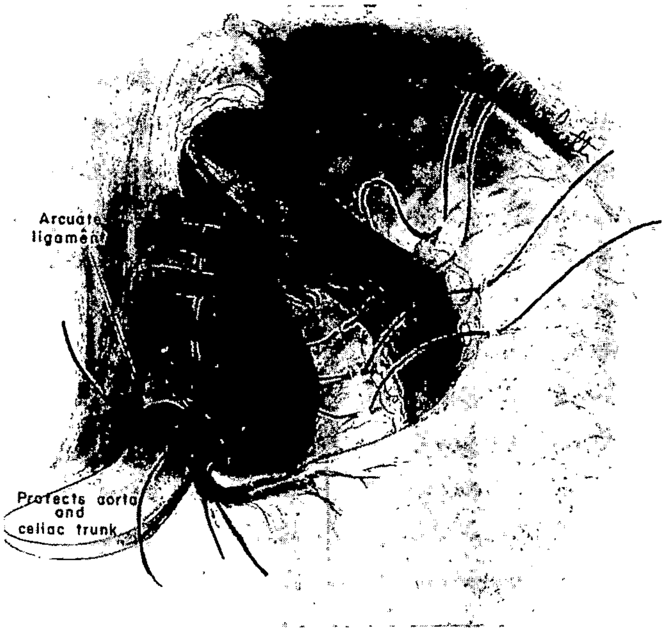

FIG. 1. Operative technique employed in each patient.

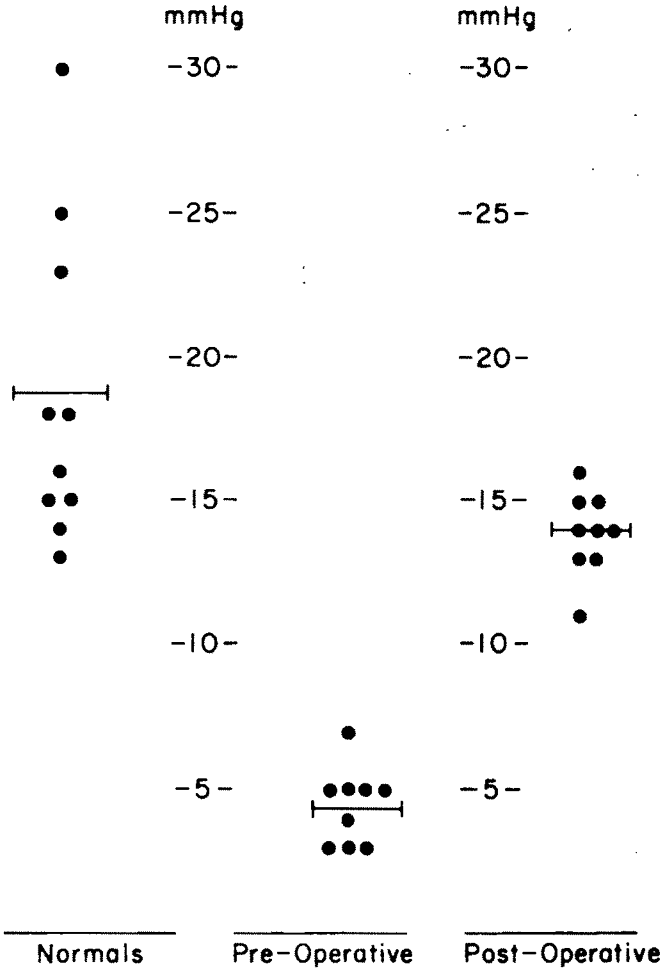

FIG. 2. Resting LES pressure in controls and patients studied before and after surgery. The LES pressure, although significantly increased following surgery ($p < .01$), remained below that recorded in controls ($p < .01$).

Discussion

The purpose of this study was to obtain a comparison of the LES pressure measurements in controls and in a group of patients with LES incompetence studied before and after surgery. The results suggest that following surgery, both resting LES pressure and the LES response to change in intra-abdominal pressure are improved significantly. However, neither the LES pressure nor the LES response to intra-abdominal pressure are returned entirely to normal following surgery. These alterations in LES pressure may explain the clinical improvement after surgery.

It was thought previously that simple repair of a hiatus hernia would be adequate to prevent gastroesophageal reflux. However, the success of these surgical procedures has been disappointing.[10,13,15] Most recently, a series of new anti-reflux operations has been described.[6,11,14] These operations have been performed even in the absence of hiatus hernia.[5] These reports have coincided with the demonstration that a hiatus hernia itself does not lead to gastroesophageal reflux, but that LES incompetence is the primary cause of gastroesophageal reflux. LES incompetence occurs independent of a hiatus hernia.[5] The mechanism by which these anti-reflux procedures improve gastroesophageal competence is unclear. The results of this study suggest that competence is improved by an increase in LES strength. This finding had been suggested previously but has not been consistently recorded.[3,7,9]

The change in LES response to increased intra-abdominal pressure following surgery may be another mechanism by which gastroesophageal competence is improved. It has been suggested that the rapid change in LES pressure associated with the change in intra-abdominal pressure was through a neural mechanism.[8] The function of this mechanism was to prevent gastroesophageal reflux during the rapid increase in intra-abdominal pressure. The LES response in normals always exceeded the rise in gastric pressure. The $\Delta S/\Delta G$ ratio was about two in normals. In patients with reduced resting LES pressures, the ratio was less than one, 0.59 ± 0.05 in this study. After clinically successful surgery, the ratio did not return to two but rather increased to approximately one.

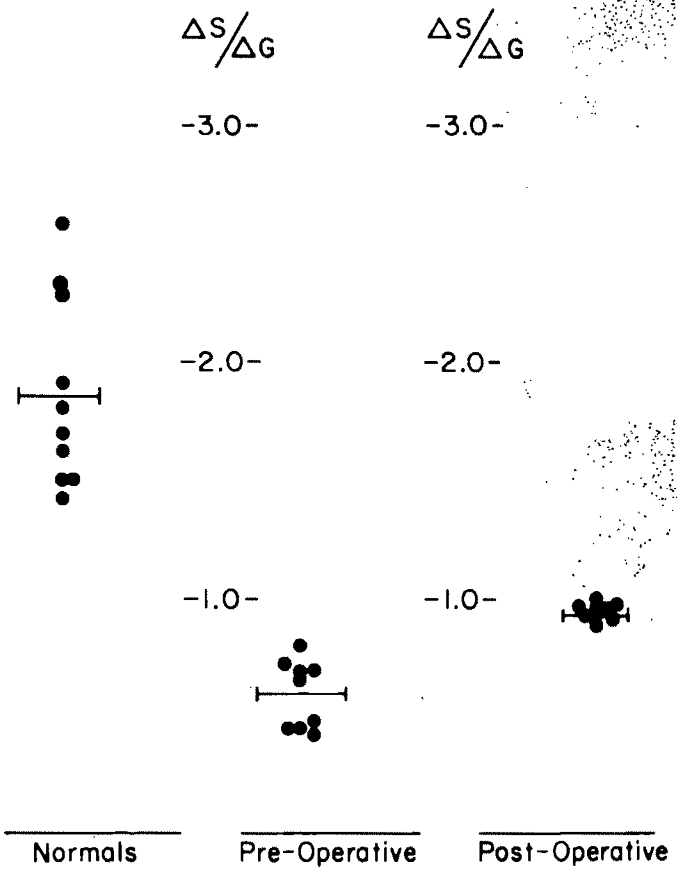

FIG. 3. The ratio of the change in LES pressure (ΔS) to the change in intra-abdominal or gastric pressure (ΔG) in controls and patients studied before and after surgery. The ratio increased significantly after surgery ($p < .01$), but remained below that recorded in controls ($p < .01$).

The results of this study suggest that clinical improvement following anti-reflux surgery may be due to both an improved resting LES competence and an improved LES response to increased intra-abdominal pressure. The mechanism of this altered LES function is unknown. These studies demonstrate simply that the clinical improvement following anti-reflux surgery may be explained by improved function of the physiological LES, the major determinant of gastroesophageal competence.

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Effect of Agitation on Platelet Aggregation and Microaggregate Formation in Banked Blood

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Blood stored at 4 C in ACD or CPD solution develops microaggregates composed primarily of fibrin and platelets. This debris has been implicated in the pathogenesis of post-traumatic pulmonary insufficiency in man. Recent work indicates that gentle agitation of the blood during storage appears to decrease debris formation. These studies were undertaken to establish more clearly the effect of agitation on debris formation. Blood was drawn in CPD from healthy young males, non-aspirin ingesting donors and stored at 4 C. One-half of the bags were gently and continuously agitated for 21 days and the other half remained stationary. At the end of the storage period, platelet counts and screen filtration pressures were measured. Agitated blood showed significantly less debris formation and significantly higher platelet counts. Gentle agitation was shown to be an effective method for preventing debris formation in banked blood.

Blood stored at 4 C in ACD or CPD solution develops microaggregates composed primarily of platelets and fibrin.[1,2,8,12] This debris in transfused blood has been shown to produce changes in pulmonary hemodynamics in animals[4,7] and has been implicated in the pathogenesis of post-traumatic pulmonary insufficiency in man.[5,9,10] Recent studies in this laboratory suggested that agitation of blood during storage appears to decrease the formation of debris.[1,2,11] The present studies were undertaken to more clearly define the effects of agitation upon debris formation in banked blood.

Materials and Methods

Ten units of fresh human blood were collected in the customary fashion in plastic bags containing CPD solution and stored at 4 C. Blood was drawn from healthy male donors between the ages of 24 and 30, with no history of aspirin ingestion for a 14-day period prior to donation.

Five units of the blood were placed in a wire basket mounted on an electrical rotating platform agitator with an 11-inch diameter platform, a velocity of 26 rpm and rotating at a 30° angle from horizontal. The entire apparatus was placed in the refrigeration unit and allowed to gently agitate, continuously for the 21-day storage period.

The remaining five units of blood were stored in the refrigeration unit for 21 days with no form of agitation.

On day 21, the following studies were performed: Platelet Counts (Model 21, Coulter Electronics); and Screen Filtration Pressure (SFP) and debris weight determinations as previously described.[6]

Results

Platelet counts of the agitated samples were considerably higher than the platelet counts for the non-agitated samples (Table 1).

Debris weights and SFP values of agitated samples were considerably less than corresponding values for non-agitated samples (Table 2).

Discussion

From analysis of Tables 1 and 2, there appears to be an inverse relationship between platelet counts and debris weights. This inverse relationship has been previously demonstrated[1,2] using serial platelet counts and debris measurements for the 21-day storage period. This is not surprising since it appears that platelet aggregation is a necessary precursor to significant debris formation.[1,2,8] Platelet aggregation may account for the decrease in platelet count observed in non-agitated stored blood.

In blood left unagitated for 21 days, separation of the red cells and the plasma occurs into approximately equal volumes. If one assumes that the platelets are entirely in the plasma fraction, then their concentration in the separated

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TABLE 1.

	Mean Day 21 Platelet Counts	p
Agitated samples	154,000/mm^3 ± 25,000	<0.001
Non-agitated samples	68,000/mm^3 ± 20,000	

TABLE 2.

	Mean Day 21 Debris Weight	p
Agitated	0.1 mg/cc ± 0.1	<0.001
Non-agitated	0.8 mg/cc ± 0.2	

fractions will be twice their concentration when dispersed in whole blood. Since aggregation can result only from platelet collisions, their initial aggregation can be closely approximated by the kinetics equation for a second order reaction: $r = k\,(\text{platelets})^2$, where 4 = the rate of aggregation, k = a constant determined by the number of platelet collisions per aggregation, and (platelets)^2 = the square of the platelet concentration. On the basis of the concentration factor alone, one would expect that since the concentration of platelets in the serum equal two times the concentration in whole blood, the rate of platelet aggregation in non-agitated blood would be four times faster than in agitated blood. Carrying this one step further then, debris formation in gently agitated blood would be expected to form debris at a rate one-fourth that of non-agitated blood.

From Table 2, we see that agitated blood formed one-eighth the debris of non-agitated. Based on the crude assumptions made in setting up the kinetics model, this would appear to be a rather good correlation between the theoretical model and the observed results. It is likely that the platelets in non-agitated blood may be found in a narrow layer within the serum fraction, thus further increasing the effective platelet concentration. If this were taken into account, our theoretical model would approximate the observed results even more closely. Another possible explanation for the discrepancy between predicted and observed values could be that platelet red cell interactions slow platelet aggregation and thus slow debris formation.

Severe agitation has been shown to induce self-aggregation of platelets,[14] possibly by rupturing the platelet membrane with subsequent ADP release. Agitation in this experiment, however, was gentle and actually reduced platelet aggregation and debris formation.

Several reports indicate that platelets are no longer viable after 3 to 5 days.[3,13] On this basis, it seems likely that agitation would be necessary for only 5 days. If, however, platelets continue to aggregate throughout the entire storage period as recent work has indicated,[1,2] then agitation would be necessary during the entire storage period.

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Arterial Injury and Massive Blood Loss:

A Case Report of Management of Pelvic Gunshot Injury With Femoro-Subscrotal-Femoral Bypass and 116 Units of Blood

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A case of massive shotgun injury to the left thigh and hip is reported. The patient received 116 units of blood, and a femoro-subscrotal-femoral vein graft was employed to save the left leg. A Teflon wool blood transfusion filter, used from the beginning of therapy, was believed to have been a major factor in preventing significant pulmonary complications.

THE SUCCESSFUL MANAGEMENT of major gunshot injuries to the pelvis can require the mobilization of the total surgical and supportive resources. The following case report describes the technical operative maneuvers and other measures employed to salvage life and limb in a young man who sustained a shotgun injury to the left groin and pelvis at close range. Despite every effort, a total of 116 pints of blood and every available measure for hemostasis were required to salvage life. A femoro-subscrotal-femoral reversed saphenous vein bypass was required to salvage the left leg.

Case Report

T.L.R., a 38-year-old black male, received a close-range shotgun blast to the lateral aspect of the left hip on the night of June 2, 1973. On arrival at the University Hospital Emergency Room shortly thereafter at 3:15 a.m., he was without blood pressure and exhibited a large soft tissue defect on the lateral aspect of the left upper thigh and buttock. Profuse bleeding continued and an emergency roentgenogram disclosed innumerable pellets concentrated in the left ischio-pubic area. The gaping wound was packed tightly, resuscitation fluids were administered to restore blood pressure and operation was begun immediately. It was found that the injury had either destroyed or deeply undermined the skin of the upper thigh to the extent that only a medial bridge of undisturbed healthy skin remained. However, while this bridge of undisturbed skin on the medial surface of the thigh was ultimately to prove crucially important in saving the left leg, at the moment of operative intervention it was the control of hemorrhage that was the primary requirement and concern. The anesthesiologists perceived immediately that massive transfusion would be required and virtually all blood transfused, which ultimately reached 116 pints, was passed through a Dacron wool blood filter[1] from the outset. This aided in protecting the lungs from "transfusion lung" during the huge blood volume replacement over the next four days.

The severe problems met in achieving hemostasis evolved from massive muscle and other soft tissue injury, severance of the saphenous and femoral vein, multiple perforations of the femoral artery, and shattering and maceration of the left ischium and adjacent sacrum. Surprisingly, the left sciatic nerve was not injured, and the left femoral nerve ultimately recovered from the blast effect and supplied innervation to the surviving elements of the left quadriceps muscle. The external and internal iliac (hypogastric) arteries were exposed and temporarily occluded. Several pellet holes in the femoral artery were sutured. The colon had not been injured.

The oozing from the pelvis was controlled as well as possible using ligatures, electrocoagulation and bone wax, plus the aforementioned temporary occlusion of the left hypogastric artery. Finally, it was decided to pack the huge space firmly with gauze rolls, bringing as much adjacent skin over the defect as possible. Through the three hour procedure the patient had received 41 units of whole blood, plus other fluids, and had maintained a good blood pressure and urine output.

In the Recovery Room his condition was initially stable, but it was presently apparent that he was losing blood steadily through the packing placed in the large soft tissue defect, which was about 10-12 cm in diameter and extended down to the sacrum. Therefore he was returned to the operating room for re-exploration, in the hope that more of the diffuse muscle ooze would have ceased and thus significant minor residual arterial bleeders could be more readily identified. Since the platelets seen in the blood smear appeared to be numerically adequate and since the blood clotted on standing, it appeared likely that uncontrolled vessels and not a bleeding diathesis was the cause of the continuing blood loss. On re-exploration of the depths of the wound under anesthesia, two additional small pellet holes were oversewn in the common femoral artery. However, fairly brisk bleeding was still arising from the pelvic fractures Bone wax and ligatures and cautery were again employed and the left hypogastric

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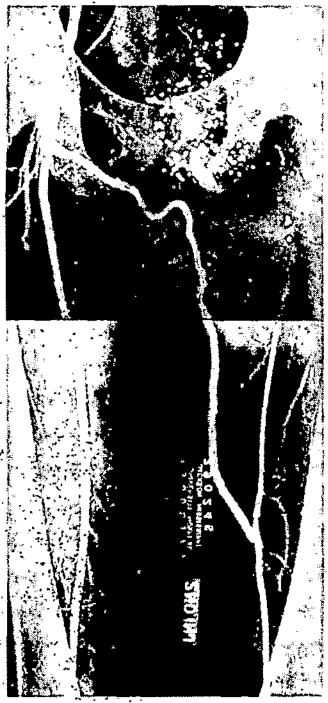

Fig. 1. Femoro-Subscrotal-Femoral Bypass. Saphenous vein bypass graft extending from the right common femoral artery, beneath the skin of the perineum just posterior to the scrotum, beneath a healthy bridge of skin on the medial surface of the left thigh, to the left superficial femoral artery in the adductor canal.

artery was exposed and ligated with No. 2 nylon. As a final measure, five large Kelly clamps were placed in such a way as to approximate the periosteum over the sites of bone fracture hemorrhage. It was appreciated that leaving instruments in the wound might lead to infection, but the wound was wide open anyway and the man's life was at stake. Gauze roll packing was again employed. The instruments were to be removed in five days.

On June 6, the fourth postoperative day, brisk bright red bleeding suddenly resumed. Exposure of the femoral artery disclosed oozing from a small, previously sutured site. This rebleeding was doubtless due to infection and, since the artery was freely exposed in the open and infected wound, it was elected to ligate this vessel just beneath the inguinal ligament and just distal to the profunda femoris artery, which was also ligated. Thus, the left hypogastric, common femoral, superficial femoral and profunda arteries had now all been ligated in the course of four separate explorations to control primary and secondary bleeding in the huge and now infected tissue defect. A total of 116 units of blood had been transfused since his admission four days earlier.

Surprisingly, the left leg and foot, while cool, remained viable and the patient maintained power and sensation in this extremity.

On June 12, however, six days later, it became apparent that the foot was no longer adequately perfused to remain viable. Therefore, the possibilities for a bypass graft that would traverse only uninfected planes were explored. It will be recalled that the anterior, lateral and posterior surfaces of the left upper thigh were either denuded or the skin undermined by an infected space. The only healthy bridge of skin in the left thigh, beneath which a bypass might be tunnelled, began just opposite the upper scrotum and extended downward. It was decided to use a reversed saphenous vein graft, taken from the healthy right leg, and to bypass from the right common femoral artery, tunnel beneath the skin of the perineum just posterior to the scrotum, and to carry the graft down to the left superficial femoral artery. This was done and it promptly restored the dorsalis pedis and posterior tibial pulses in the left foot. A late postoperative arteriogram is presented in Fig. 1.

The large soft tissue defect was closed somewhat by pulling together healthy debrided muscle with chromic catgut, and by reducing the skin defect to the extent possible. Drainage was maintained over the ensuing months until rehabilitation was judged on May 7, 1974 to be largely complete with closure of all but a small sinus tract.

Comment

The successful outcome of this case reflects many of the major advances in surgical resources and care that have been developed in recent years. First, the support of this patient by the anesthesiologists during and following the several operations was a model of effective utilization of continuous arterial pressures, central venous pressures, pulmonary wedge pressures, arterial blood gases, the electrocardiogram, serial plasma electrolyte measurements, urine output and the general assessment of the overall condition of the patient at all times. The use of the Dacron wool blood filter from the outset protected the lungs during the subsequent transfusion of 116 units of blood. This excellent support of the patient provided the optimal possible respiration and cardiac output during the five operations that were required for the management of the massive injury. Secondly, the use of the saphenous vein bypass permitted salvage of the left leg in this young man. With ingenuity, one can extend a bypass arterial graft from almost any region of the body to another. The graft will usually remain patent if there is a sufficient head of pressure proximally, a sufficient pressure differential, and good distal run-off. The saphenous vein has proved to be extremely useful as an arterial substitute in a wide variety of circumstances.

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Benign Small Bowel Tumor

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The clinical record and histologic sections of 84 cases of benign small bowel tumor are reviewed. Manifestations of systemic diseases, congenital anomalies, and lesions of either the ileocecal valve or periampullary region were excluded. In the same time span there were 96 small bowel malignancies. Clinical presentation, pathologic findings, management and result are compared to the collected published experience of about 2000 cases. There were 36 leiomyomas, 22 lipomas, 9 angiomas, 6 neurofibromas and 4 fibromas. Thirty-six men and 48 women were affected; the majority in their fifth and sixth decade. Seventy-eight were operative and 6 autopsy diagnoses. The most common symptom was obstruction (42%) followed by hemorrhage (34%) and pain (22%), relative frequency differing for the various specific tumors. There were rarely significant physical findings. A diagnosis of small bowel tumor was made radiologically in 30 patients. Because of the nonspecificity of other signs and symptoms, an acute awareness of the possibility of small bowel tumor is mandatory for preoperative anticipation of the diagnosis. Local resection was performed in all with no deaths or significant postoperative complications.

BENIGN TUMORS are quite rare in the small bowel[15] and these lesions usually become clinically apparent only when they produce complications such as hemorrhage or obstruction.

Since the first collective review of benign small bowel tumors by Hearteaux[11] in 1899, information about the incidence and behaviour of these tumors has accrued slowly. The most recent extensive study of the literature was of 1340 cases by River *et al.*[16] in 1955.

The records of The New York Hospital-Cornell Medical Center were reviewed for the period between 1932 and 1972. There were 180 cases of primary tumors of the small bowel. Eighty-four of these were benign, including seven previously reported by Eckel[8] in 1948. Manifestations of systemic diseases, such as Peutz-Jegher's syndrome and Von Recklinhausen's disease were excluded as were ectopic pancreas, periampullary tumors, and ileococecal valve tumors. All carcinoid tumors were considered to be malignant. Six types of benign tumors were found; leiomyomas, lipomas, angiomas, adenomas, neurofibromas, and fibromas. Their anatomic distribution is given in Table 1.

This communication reports and analyses these 84 cases. Cumulative data from the collective review of River *et al.* and 657 cases[1,2,4-7,9,12-14,17,19,21,24] from major reviews since 1955 are tabulated, presented, and compared with our experience.

Clinical Presentation

Thirty-six of the tumors appeared in male patients and 48 in females, similar to a near equal sex distribution in reported series.[1,2,6,9,12,16] Thirty-one per cent were in their sixth and 28% in their fifth decade, not notably different from the age range of other series.[1,2,7,9,12,14,16] Racial distribution was 90% Caucasian, 9% Negro, and 1% Oriental, approximating the admission pattern of The New York Hospital. The eighty-four tumors occurred in 83 patients; one patient had a jejunal leiomyoma detected and removed eight years following resection of a similar tumor in the duodenum. The symptoms that attracted clinical attention are given in Table 2. Six of these tumors were discovered as incidental autopsy findings, four of these thought in retrospect to have caused symptoms. The remaining tumors were sufficiently symptomatic to require operation.

Obstruction

Obstruction was the most common symptom in the group as a whole, and was evident in one form or another in 42% (35) of the total. Most often the obstruction was evidenced by crampy intermittent abdominal pain. Often the symptoms abated and allowed study of the patient and elective surgery to be performed. Over half (20) of the patients, however, entered the hospital and had an emergency laparotomy done for unrelieved obstruction. Of these patients 15 had had prior symptoms of intermittent obstruc-

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TABLE 1. *Distribution of Benign Tumors of the Small Intestine*

Histologic Type	Total Number	Duodenum	Location Jejunum	Ileum
84 New York Hospital Cases				
Leiomyoma	36	7 (19%)	14 (39%)	15 (42%)
Lipoma	22	7 (32%)	3 (14%)	12 (54%)
Angioma	9		3 (33%)	6 (66%)
Adenoma	7	2 (28%)		5 (72%)
Neurofibroma	6	1 (17%)	1 (17%)	4 (66%)
Fibroma	4		1 (25%)	3 (75%)
	84	17 (20%)	22 (26%)	45 (54%)
1721 Collected Cases Where Location was Specified				
Leiomyoma	380	73 (19%)	168 (44%)	139 (37%)
Lipoma	301	72 (24%)	54 (18%)	175 (58%)
Angioma	212	18 (8%)	99 (47%)	95 (45%)
Adenoma	245	97 (39%)	61 (25%)	87 (36%)
Neurofibroma	76	12 (16%)	24 (32%)	40 (52%)
Fibromas	153	8 (5%)	26 (18%)	119 (77%)
Fibromyomas	64	12 (18%)	17 (26%)	35 (56%)
Myofibromas	10	1 (10%)	3 (30%)	6 (60%)
Myxomas	6		1 (16%)	5 (84%)
Villous Adenomas	15	9 (60%)	3 (20%)	3 (20%)
Neurolemmomas	2		1 (50%)	1 (50%)
Polyps	245	61 (25%)	63 (26%)	121 (49%)
Fibroadenomas	12	4 (33%)	2 (17%)	6 (50%)
	1721	367 (21%)	522 (30%)	832 (49%)

tion and only five underwent emergency surgery for obstruction without prior symptoms.

Hemorrhage

Twenty-eight patients (34%) presented with bleeding, in 13 severe enough to require emergency laparotomy. Hemorrhage has been reported in from 9% to 58% of previous series.[2,5,7,10,14,16,19,20,22] Hemorrhage has generally been most common from hemangiomas and leiomyomas; other tumors do cause bleeding but less often.[2,9,14,16]

Pain

A significant number of patients, including most of those noted above to have chronic obstructive symptoms, presented with some pain. In 18 (22%) pain was a predominant symptom. It was always of a colicky nature and usually followed meals. This closely resembles the pain described by others[16,19] although a burning component has at times caused false diagnosis of peptic ulcer disease.[19] The reported incidence of significant pain from benign small bowel tumors ranged from 12% to 36%.[2,5,7,10,14,16,19,20,22]

Weight Loss

Weight loss is an uncommon symptom from small bowel tumors. In our experience only one patient reported preoperative weight loss. This patient had a duodenal tumor and regained his weight following removal. Among the patients observed with acute intestinal obstructions, weight loss may be common especially when the obstruction is high in the small bowel. This loss of weight however is transient and corrected by replacement of fluid losses from vomiting. Other reports except for River's cumulative review also indicate that weight loss is a rare symptom.

Specific Tumors

Leiomyomas. Leiomyomas are intramural tumors composed of whorls of smooth muscle closely resembling the normal muscularis. These tumors are usually well circumscribed but ordinarily lack a true connective tissue capsule. They grow by expansion with compression of lumen

TABLE 2. *Clinical Features of Benign Small Bowel Tumors*

Tumor	Total Cases	Bleeding	Pain	Acute Obstruction Intussusception	Acute Obstruction Other	Chronic Obstruction	Weight Loss	Mass
84 New York Hospital Cases								
Leiomyoma	36	14(39%)	6 (17%)	3 (8%)	2 (5%)	11 (30%)		2 (5%)
Lipoma	22	6 (27%)	5 (23%)	7 (31%)	2 (1%)	10 (45%)		
Angioma	9	6 (67%)	3 (33%)			0 (0%)		
Adenoma	7	2 (29%)	1 (14%)	3 (42%)		2 (29%)	1 (12%)	
Neurofibroma	6		2 (33%)	3 (50%)		4 (67%)		
Fibroma	4		1 (25%)		0 (0%)	3 (75%)		0 (0%)
Totals	84	28 (34%)	18 (22%)	16 (19%)	4 (5%)	30 (37%)	1 (1%)	2 (2%)
Collected Cases (1047 tumors of similar cell types in which adequate data is available for tabulation)								
Leiomyoma	196	87 (45%)	106 (54%)	25 (13%)	27 (29%)	57 (29%)	26 (13%)	51 (26%)
Lipoma	224	32 (14%)	35 (16%)	114 (51%)	22 (10%)		21 (9%)	56 (25%)
Angioma	134	55 (41%)	42 (31%)	18 (13%)	20 (15%)		9 (7%)	14 (10%)
Adenoma	232	70 (30%)	50 (25%)	119 (51%)	31 (13%)		39 (17%)	62 (27%)
Neurofibroma	90	32 (36%)	37 (41%)	7 (8%)	20 (22%)		5 (6%)	22 (25%)
Fibroma	163	30 (18%)	116 (69%)	105 (63%)	33 (20%)		32 (19%)	45 (27%)
Totals	1037	306 (30%)	386 (38%)	388 (38%)	183 (18%)		132 (13%)	250 (24%)

and stretching of the mucosa as the mass increases in size. Ulceration is due to compromise of attenuated blood vessels rather than invasion. The bulk of the tumor may be on the serosal side of the bowel and the lesion may have a dumbbell shape due to the increased resistance to expansion by the muscularis as compared to the serosa and submucosal areolar connective tissue.

Some nuclear pleomorphism may be seen in benign tumors. A diagnosis of malignancy is based on increased mitotic activity indicated by more than one mitotic figure per high power field. Palisading of nuclei into rows is frequently seen in leiomyomas and should not be considered characteristic of a nerve sheath tumor which is an extremely rare entity in the intestine. Hyalinization of variable degree may be observed in some leiomyomas which is undoubtedly the basis of designations such as fibromyoma or myofibroma in other reports.

These tumors were the most prevalent of all cell types in both our own and the previously reported experiences. The distribution through the small bowel was rather uniform, if the shorter duodenal length is considered. Both bleeding and pain were frequent presenting symptoms,[3,16] each occurring in over 40% of patients (combining collected cases with our own). Acute obstruction was common, occurring in over one-fourth of patients, but was less often due to intussusception than with some other tumors. Perforation is very rare (seven cases have been reported), but except for one neurofibroma, small bowel tumors that do perforate have been universally leiomyomas.[16] Peak age of occurrence is in the fifth decade[16] and there is no sexual predominance.

Lipomas. Intestinal lipomas are well-circumscribed masses of adult adipose tissue, occasionally surrounded by a delicate collagen capsule. Most of these lesions arise within the submucosa and they grow by expansion with compression of the lumen. It seems likely that many of these lesions are hamartomas rather than neoplasms. Most lipomas have scant vasculature but in some lesions, vessels are more prominent and these are occasionally designated angiolipomas. Fat necrosis may be prominent in some tumors and the presence of foreign body type cells with fat necrosis should not be mistaken for liposarcoma.

Over half of the lipomas reported, in both our own and cumulative experience were in the ileum. There was a high incidence (51% of those in previous reports and 31% of our patients) of intussusception. Nearly half of our patients had symptoms of chronic intermittent obstruction. Bleeding was less frequent than in the other common tumors, being found in only 14% of collected cases. Fifteen of our 22 patients were men. Our peak age of occurrence was the seventh decade, in River's cases more patients were in their sixth decade.

Angiomas. True angiomas are discrete, well circumscribed or encapsulated masses, composed of blood vessels. Capillaries and thin-walled veins usually predominate, but arteries and arterioles may be seen. Some of these lesions are probably hamartomatous arteriovenous malformations rather than vascular neoplasms, but their circumscription distinguishes them from disorders such as Osler-Weber-Render syndrome. The lesions are usually in the submucosa.

Angiomas were the third most common of the tumors in our series, and fourth among collected cases, comprising about 10–12% of each group. Bleeding was the predominant presentation occurring in 6 of our 9 patients, and slightly less often in other reports. Most of the patients were in their seventh decade. There were five men and four women. Pain has been reported in a substantial number of cases and was present in three of our nine cases.

Adenomas. Adenomas are neoplasms of surface epithelium usually in the form of a nodular mass with a stalk composed of normal mucosa and submucosa. The rare epithelial tumors of small bowel with a uniform villous or papillary pattern were associated with invasive carcinoma in all instances in our experience. Some lesions originally classified as adenomas proved to be inflammatory polyps on review, and are not included in our report. Adenomas differ from the polyps seen in Peutz-Jeghers syndrome in that the latter have a smooth muscle component suggesting that they are hamartomas.

There were only 7 adenomas in our series. Adenomas represent 12 percent of all reported cases. When ours and collected reports are combined, there is a fairly even age distribution and acute obstruction, usually by intussusception, was the predominant (64%) presentation. A disproportionate number (39%) were found in the duodenum.

Neurofibromas. Neurofibromas are isolated tumors of nerve sheath origin usually unencapsulated and poorly circumscribed lesions composed of wavy, fibrillary elements. These lesions are identical to those seen in systemic neurofibromatosis (von Recklinghausen's disease). They are found in submucosa, muscularis or serosa, reflecting the distribution of nerve tissue.

There were 6 neurofibromas in our series; they are somewhat less common in total collected cases. They usually occur in the ileum, and bleeding (36%) is more frequent than other symptoms. Intussusception occurred in 3 of our cases but was reported in only 7 of 90 neurofibromas in the cumulative review. Most reported cases have been in their fifth or sixth decade. One instance of perforation has been reported.[16]

Fibromas. Fibromas are circumscribed tumors consisting of dense thick collagen bundles and variable numbers of mature appearing fibroblasts. These tumors may occur in submucosa, muscularis or serosa. In some instances scar tissue may be indistinguishable from a fibroma but usually the fibroma shows a greater degree of circumscription.

Four small intestinal fibromas were found in our material, all in male patients; three of these were in the ileum. From the collective review it may be seen that 65% of fibromas cause intussusception and obstruction. Pain was the second most common finding. Fibromas are mainly found in adults with evenly distributed age occurrence.

Diagnosis

The diagnosis of small bowel tumors is difficult and most often only established at the operating table. Tumors of the stomach and the large bowel are fairly easily diagnosed by conventional barium x-rays or by direct visualisation through the gastroscope or colonoscope. The large volume of succus entericus, the length of the small bowel and rapid passage of the medium through the intestine tend to make the x-ray diagnosis of small bowel tumors difficult and not easily reproducible. In our cases a radiological diagnosis of small bowel tumor was made 30 times.

The most common symptoms of small bowel tumor, obstruction and bleeding are also quite nonspecific and do not necessarily lead to the correct diagnosis. In the case of small bowel obstruction, the most common cause is intestinal adhesion or hernias. In the case of blood in stools the most common sources are in the colon, anus, stomach or duodenum.

The clinician however should become suspicious when a patient with no previous operation has intermittent bouts of small bowel obstruction, or intermittent crampy abdominal pain. Similarly the patient with occult blood in the stool and normal examination of the upper and lower gastrointestinal tract should be suspect. The sign of frankly bloody stool or currant jelly stool as seen in infarct with intussusception may of course be pathognomic. The clinician who encounters patients of this type must bear the possibility of small bowel tumor in mind, and also recognize that the diagnosis may not be made except through an operation. Intussusception in adults is almost always caused by a tumor, benign or malignant.

Treatment and Results

All of the tumors diagnosed intraoperatively were treated by local segmental or wedge resection. There were no deaths in operation or operative admission. No patient suffered significant postoperative complications.

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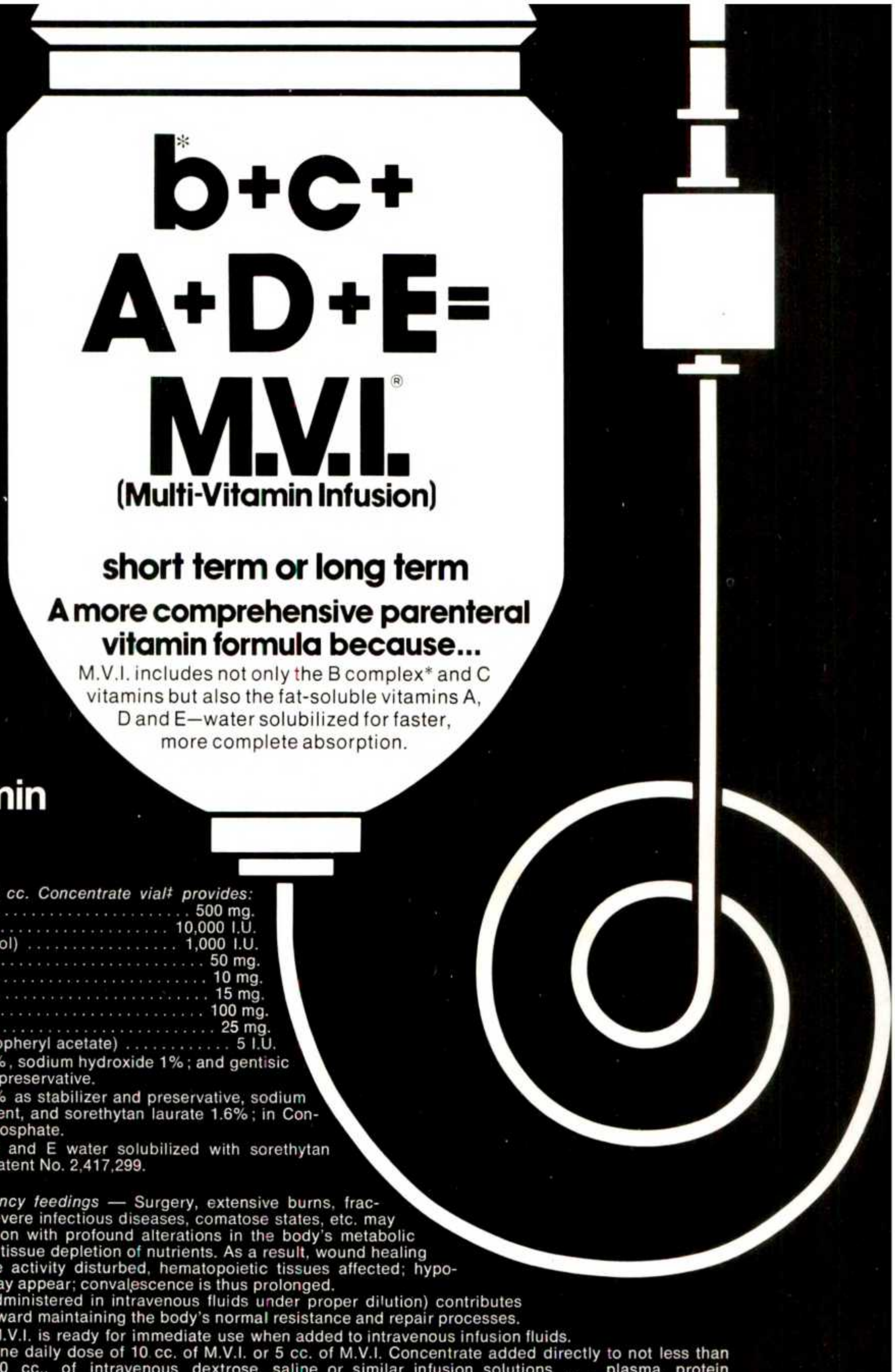

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d ethanolamide 2% as preservative.

h propylene glycol 30% as stabilizer and preservative, sodium
roxide for pH adjustment, and sorethytan laurate 1.6%; in Con-
trate as riboflavin-5-phosphate.

soluble vitamins A, D and E water solubilized with sorethytan
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EF SUMMARY

ICATIONS: *in emergency feedings* — Surgery, extensive burns, frac-
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voke a "stress" situation with profound alterations in the body's metabolic
nands and consequent tissue depletion of nutrients. As a result, wound healing
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teinemia and edema may appear; convalescence is thus prolonged.
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mum vitamin intake toward maintaining the body's normal resistance and repair processes.

ECTIONS FOR USE: M.V.I. is ready for immediate use when added to intravenous infusion fluids.
intravenous feeding, one daily dose of 10 cc. of M.V.I. or 5 cc. of M.V.I. Concentrate added directly to not less than
cc., preferably 1,000 cc., of intravenous dextrose, saline or similar infusion solutions . . . plasma, protein
rolysates, etc.

CAUTION: Allergic reaction has been known to occur following intravenous administration of solutions contain-
thiamine.

TION: Not to be given as a direct undiluted intravenous injection as it may give rise to dizziness, faintness, etc.

RAPEUTIC NOTE: Intravenous use should be discontinued as early as practical in favor of an intramuscular or oral
min preparation, if deemed advisable.

V SUPPLIED: M.V.I. — 10 cc. ampuls, boxes of 25 and 100.
.I. CONCENTRATE — 5 cc. vials, boxes of 25. Available in 100's only.

* M.V.I. formula contains vitamins B_1, B_2, niacinamide, dexpanthenol and B_6. If needed, vitamin K, vitamin B_{12} and folic acid may be optional additions to parenteral nutrition

Help allay the
Excessive Anxiety
that may heighten
Postop Pain

Vistaril I.M. (hydroxyzine HCl). It helps allay the excessive anxiety that can heighten the patient's perception of pain, and helps assure calm and cooperative patients. Vistaril I.M. also helps minimize secondary postoperative complaints, and often relieves postoperative confusion.

Vistaril I.M. may enhance the effect of injectable analgesics, such as meperidine,

significant depressant effects on respiratory or circulatory function and often reduces postoperative emesis.

It is physically compatible with most commonly used analgesics, and can be mixed with them in the same syringe.

Alone, or as an adjunct for use in the management of postoperative pain, the maximum recommended dosage of Vistaril I.M. is 100 mg. While the analgesic dosage needed will usually be reduced, the actual dosage of Vistaril I.M. should be titrated against the individual patient's clinical response.

Vistaril® I.M.
(hydroxyzine HCl)
100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

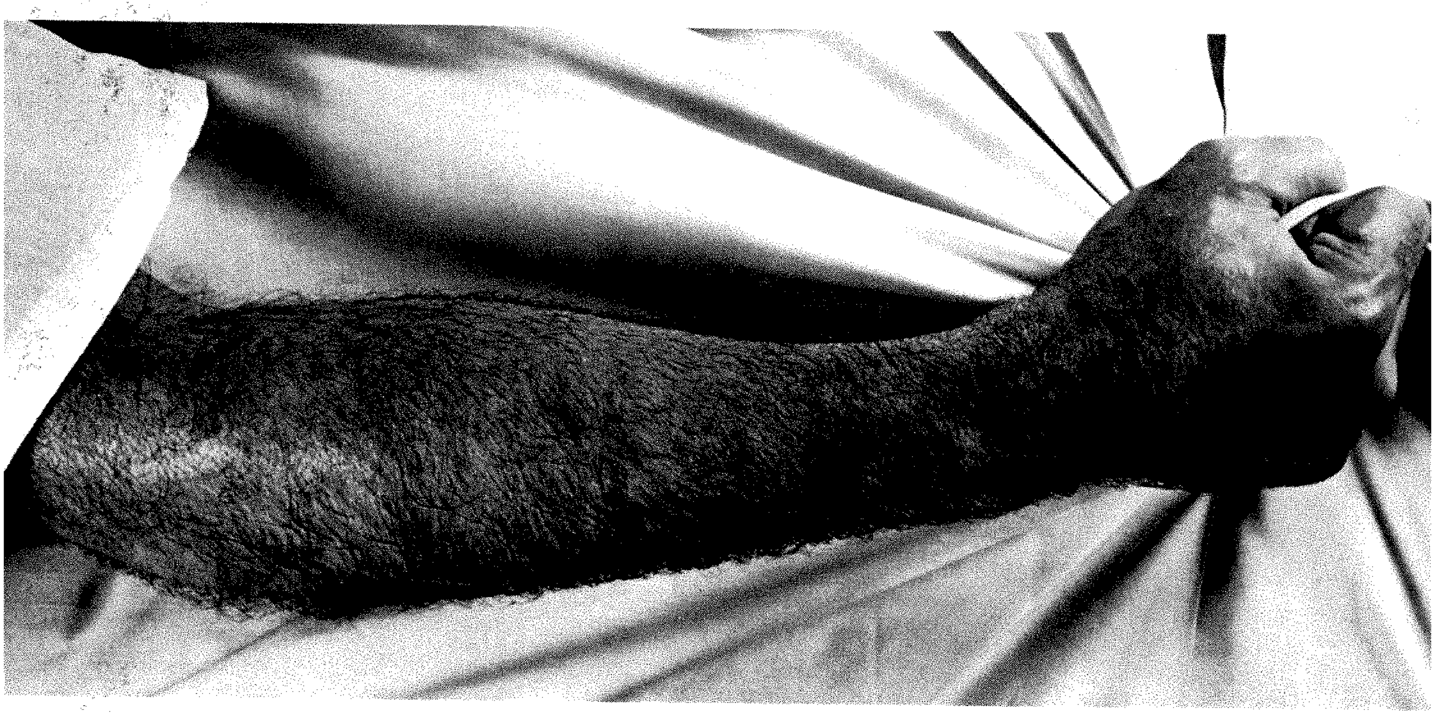
Pfizer LABORATORIES DIVISION
PFIZER INC

Please see Brief Summary on following page for contraindications, precautions and adverse reactions.

Vistaril® I.M.
(hydroxyzine HCl)

100 mg./2 ml., 50 mg./ml. and 25 mg./ml.
Vials and Isojects®

helps relieve the anxiety associated with postoperative pain
may enhance narcotic effect
offers proved antiemetic action



Brief Summary
VISTARIL® (hydroxyzine hydrochloride) Intramuscular Solution
For Intramuscular Use Only

Contraindications: Hypersensitivity to hydroxyzine. The solution for intramuscular use *must not* be injected subcutaneously, intra-arterially, or intravenously.

Hydroxyzine, when administered to the pregnant mouse, rat, and rabbit, induced fetal abnormalities in the rat at doses substantially above the human therapeutic range. Clinical data in human beings are inadequate. Until adequate data are available to establish safety in early pregnancy, hydroxyzine is contraindicated during this period.

Precautions: *Hydroxyzine may potentiate the action of central nervous system depressants such as narcotics and barbiturates.* In conjunctive use, dosage for these drugs should be decreased as much as 50%. Because drowsiness may occur, patients should be cautioned against driving a car or operating dangerous machinery. The usual precautions for intramuscular injection should be followed; soft-tissue reactions have rarely been reported when proper technique has been used. Hydroxyzine intramuscular solution should be injected well within the body of a relatively large muscle. In adults, the preferred sites are the upper outer quadrant of the buttock (i.e., gluteus maximus), or the mid-ateral thigh. In children, preferably the mid-lateral muscle of the thigh. In infants and small children, the upper outer quadrant of the gluteal region should only be used when necessary, as in burn patients, in ord to minimize the possibility of damage to the sciatic nerve. The deltoid area should be used only if well developed, such as in certain adults a older children, and only with caution to avoid radial nerve injury. Injections should not be made in the lower and middle thirds of the upper arm. Aspiration is necessary to help avoid intravascular injectio

Adverse Reactions: Drowsiness may occur; if so, it is usually transitor and may disappear in a few days of continued therapy or upon dosage reduction. Dryness of the mouth may occur with higher doses. Involuntary motor activity, including rare instances of tremor and convulsions, has been reported, usually with higher than recommended dosage.

Supply: Vistaril (hydroxyzine HCl) Intramuscular Solution: 25 mg./ml.-10 ml. vial; 50 mg./ml.—2 ml. and 10 ml. vial; Isoject®, 25 mg./ml. and 50 mg./ml., 1 ml. fill; 100 mg./2 ml., 2 ml. fill.
Military Depot: NSN 6505-00-052-1367 (50 mg./ml., 10 ml. vial)
VA Depot: NSN 6505-00-052-1367B (50 mg./ml., 10 ml. vial)

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Effective performance in postsurgical and other serious susceptible hospital infections

Bacteriologically controlled studies demonstrated efficacy in patients with:

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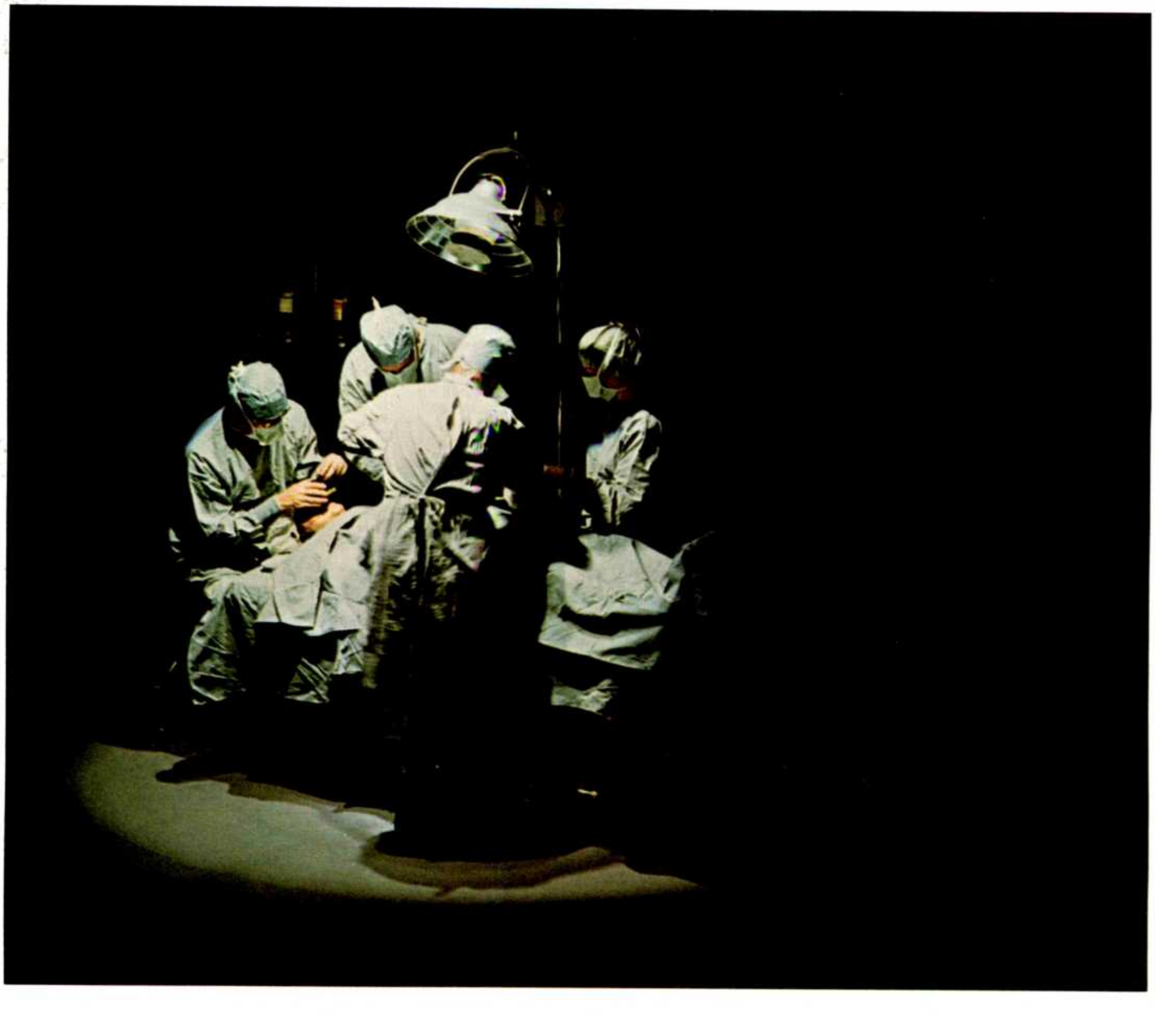
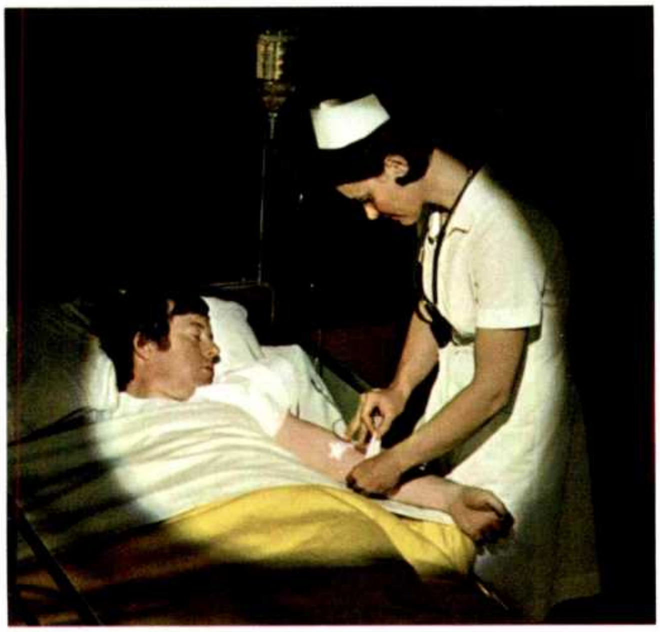




Low incidence of venous irritation on I.V. administration... well tolerated locally

In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low. *Controlled studies* in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly.

Cephalosporins are reported to produce maculopapular rash, urticaria, reactions resembling serum-sickness and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

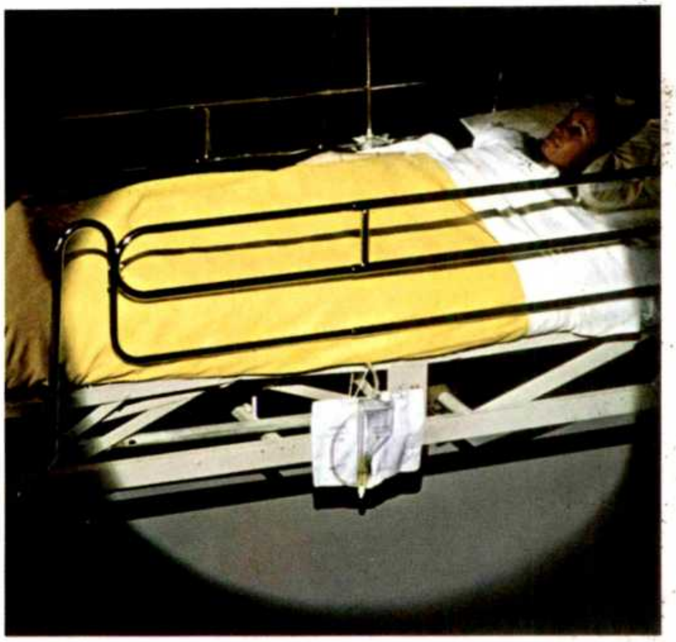
In penicillin-allergic patients, cephalosporins should be used with great caution. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins, and there are instances of patients who have had reactions to both drugs (including fatal anaphylaxis after parenteral use).

Flexible Dosage: adjustable to fit severity of infection and renal status of patient:

The usual adult dose of Cefadyl is 0.5 Gm. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. Doses up to 12 Gm. daily may be used in very serious or life-threatening infections.

No nephrotoxicity reported during extensive clinical trials

In fact, when Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported. However, renal status of patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate. Rises in BUN have been observed; their frequency increases in patients over 50 years old. (See Dosage, Adults—in Prescribing Information on last page.)



Cefadyl® IV/IM
sterile cephapirin sodium

Please see next page for Prescribing Information.

BRISTOL

Cefadyl® IV/IM
sterile cephapirin sodium

Effective performance in surgical and other serious susceptible hospital infections

CEFADYL® (sterile cephapirin sodium) 7628 DIRO-07 July 1974

Description. Cefadyl (sterile cephapirin sodium) is a cephalosporin antibiotic intended for intramuscular and intravenous administration only. It is supplied as the sodium salt of 7-[α-(4-pyridylthio)-acetamido]-cephalosporanic acid. Each 500 mg. contains 1.18 milliequivalents of sodium.

Actions. *Human Pharmacology*—Following intramuscular administration of single 500-mg. and 1-Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

Cefadyl and its metabolites were excreted primarily by the kidneys. Antibiotic activity in the urine was equivalent to 35% of a 500-mg. dose 6 hours after I.M. injection, and to 65% of a 500-mg. dose 12 hours after injection. Following an I.M. dose of 500 mg., peak urine levels averaged 900 mcg./ml. within the first 6 hours.

Following rapid intravenous administration of single 0.5-Gm., 1-Gm., and 2-Gm. doses, peak serum levels of 35, 67, and 129 mcg./ml. respectively, were attained at 5 minutes, declining to 6.7, 14.0, and 31.7 mcg./ml. respectively, at 30 minutes and 0.27, 0.61, and 1.11 mcg./ml. respectively, at 3 hours.

Seventy percent of the administered dose was recovered in the urine within 6 hours. Repetitive intravenous administration of 1-Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—In vitro tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro:*

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis,* are relatively resistant.)

Staphylococci, including coagulase-positive, coagulase-negative, penicillinase, and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli,* Klebsiella species.

Most strains of enterobacter and indole-positive Proteus (*P. vulgaris, P. morganii, P. rettgeri*) are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima, and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections, and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organism and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution, or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce th following reactions: maculopapular rash, urticaria, reactions resembling seru sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to b associated with other allergic reactions. These reactions are most likely to occu in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leuko penia, anemia were reported. Some individuals, particularly those with azotemi have developed positive direct Coombs test during therapy with other ceph losporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin hav been reported.

Kidney—Rises in BUN have been observed; their frequency increases in pa tients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramus cularly or intravenously. The lower dose of 500 mg. is adequate for certain infec tions, such as skin and soft tissue and most urinary tract infections. However, th higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Gram daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patient with reduced renal function (moderately severe oliguria or serum creatinine abov 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./K of cephapirin every 12 hours. Patients with severely reduced renal function an who are to be dialyzed should receive the same dose just prior to dialysis an every 12 hours thereafter.

Children—The dosage is in accordance with age, weight, and severity of infec tion. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb. administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treat ment of children under the age of three months the relative benefit/risk shoul be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at leas 10 days.

Where indicated, surgical procedures should be performed in conjunction wit antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intra venous routes.

Intramuscular Injection—The 1-Gm. vial should be reconstituted with 2 ml. o Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients wit bacteremia, septicemia, or other severe or life-threatening infections who may b poor risks because of lowered resistance resulting from such debilitating condi tions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy particularly if shock is present or impending. If patient has impaired renal func tion, a reduced dose may be indicated (see *Dosage, Adults*). In conditions suc as septicemia, 6 to 8 Gm. per day may be given intravenously for several days a the beginning of therapy; then, depending on the clinical response and laborator findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment an multiple sites have been involved, daily doses up to 12 Gm. have been used.

For patients who are to receive cephapirin intravenously it is convenient to us the 1-Gm., 2-Gm., or the 4-Gm. vial (See Precautions).

Intermittent Intravenous Injection—The contents of the 1-Gm. vial should b diluted with 10 ml. or more of diluent and administered slowly over a 3- to 5 minute period or may be given with intravenous infusions.

The 2-Gm. vial should be diluted with Dextrose Injection, U.S.P. or Sodiu Chloride Injection, U.S.P. When only 20 to 25 ml. are added, Sterile Water fo Injection, U.S.P. may be used. The table below gives concentrations for variou diluent volumes.

Diluent Added (ml.)	*Solution Concentration*	*Grams per ml.*
100	1 Gm. per 50 ml.	0.020
50	1 Gm. per 25 ml.	0.040
20	1 Gm. per 10 ml.	0.100

Intermittent Intravenous Infusion with Y-Tube—Intermittent intravenous infusio with a Y-type administration set can also be accomplished while bulk intravenou solutions are being infused. However, during infusion of the solution containin Cefadyl (sterile cephapirin sodium), it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to th volume of the solution containing Cefadyl so that the calculated dose will be infused. When a Y-tube hookup is used, the contents of the 4-Gm. vial of cephapiri should be diluted by addition of 40 ml. of Sterile Water for Injection, U.S.P. 5 percent Dextrose Injection, U.S.P., or Sodium Chloride Injection, U.S.P.

Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added t the solutions listed below under *Stability*. The choice of solution and volum should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability:* After reconstitution, it is stable for 12 hours at roo temperature or 10 days under refrigeration when reconstituted with Sterile Wate for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5 Durin these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

Compatibility with the Infusion Solutions: Cefadyl is stable and compatible fo 24 hours at room temperature at concentrations between 2 mg./ml. and 30 mg./ml in the following solutions:

Sodium Chloride Injection, U.S.P., 5% W/V Dextrose in Water, U.S.P., Sodiu Lactate Injection, U.S.P., 5% Dextrose in Normal Saline, U.S.P., 10% Invert Suga in Normal Saline, 10% Invert Sugar in Water, 5% Dextrose + 0.2% Sodium Chloride Injection, U.S.P., Lactated Ringer's with 5% Dextrose, 5% Dextrose + 0.45% Sodium Chloride Injection, U.S.P., Ringer's Injection, U.S.P., Lactated Ringer' Injection, U.S.P., 10% Dextrose Injection, U.S.P.

Supply. Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapiri sodium equivalent to 1 Gm., 2 Gm., or 4 Gm. cephapirin. NDC 0015-7628—1-Gm. vial. NDC 0015-7629—2-Gm. vial. NDC 0015-7630—4-Gm. vial.

For information on package sizes available, refer to the current price schedule.

BRISTOL

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*Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

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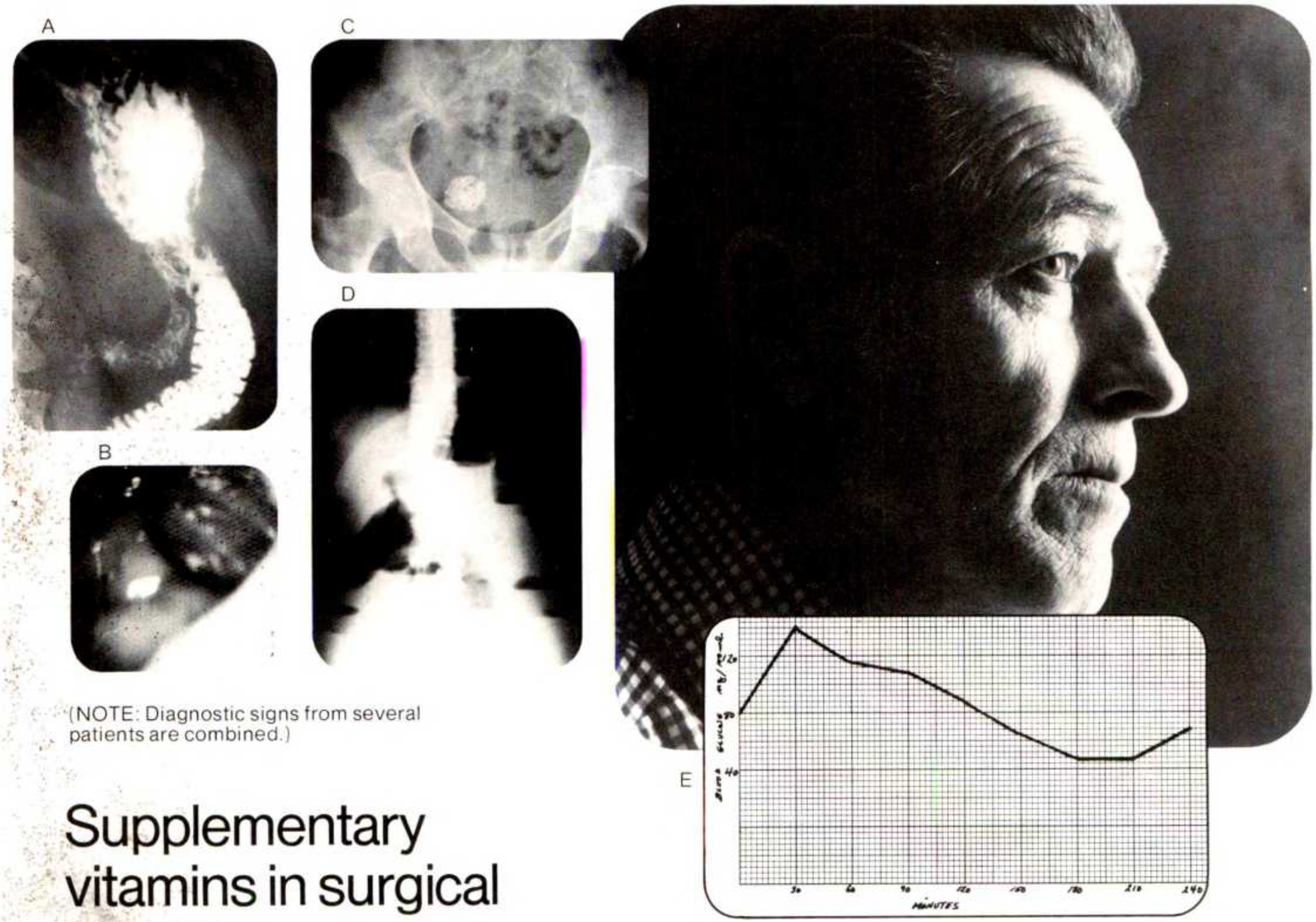

(NOTE: Diagnostic signs from several patients are combined.)

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BEROCCA® TABLETS IS THERAPY
Rx

With balanced, high potency vitamin B-complex and 500 mg vitamin C
Virtually no odor or aftertaste
Low priced Rx formula

**Diagnosis appears on next page.*

See next page for summary of Product Information.

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Berocca Tablets
#100
Sig: 1 Tab
B.I.D.

DIAGNOSIS: Postgastrectomy (Billroth No. II) and its complications: (A) Barium meal showing gastrojejunostomy; (B) Endoscopy showing gastrojejunostomy; (C) X-ray of the pelvis showing osteoporosis; (D) Flat plate of the abdomen showing small bowel obstruction; (E) Glucose tolerance test showing late hypoglycemia.

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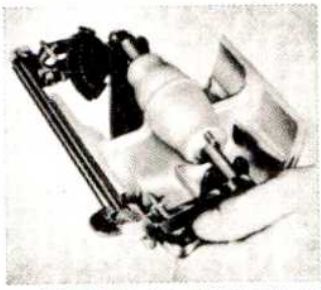

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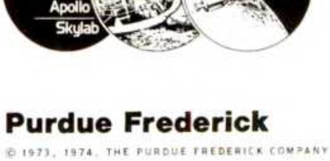

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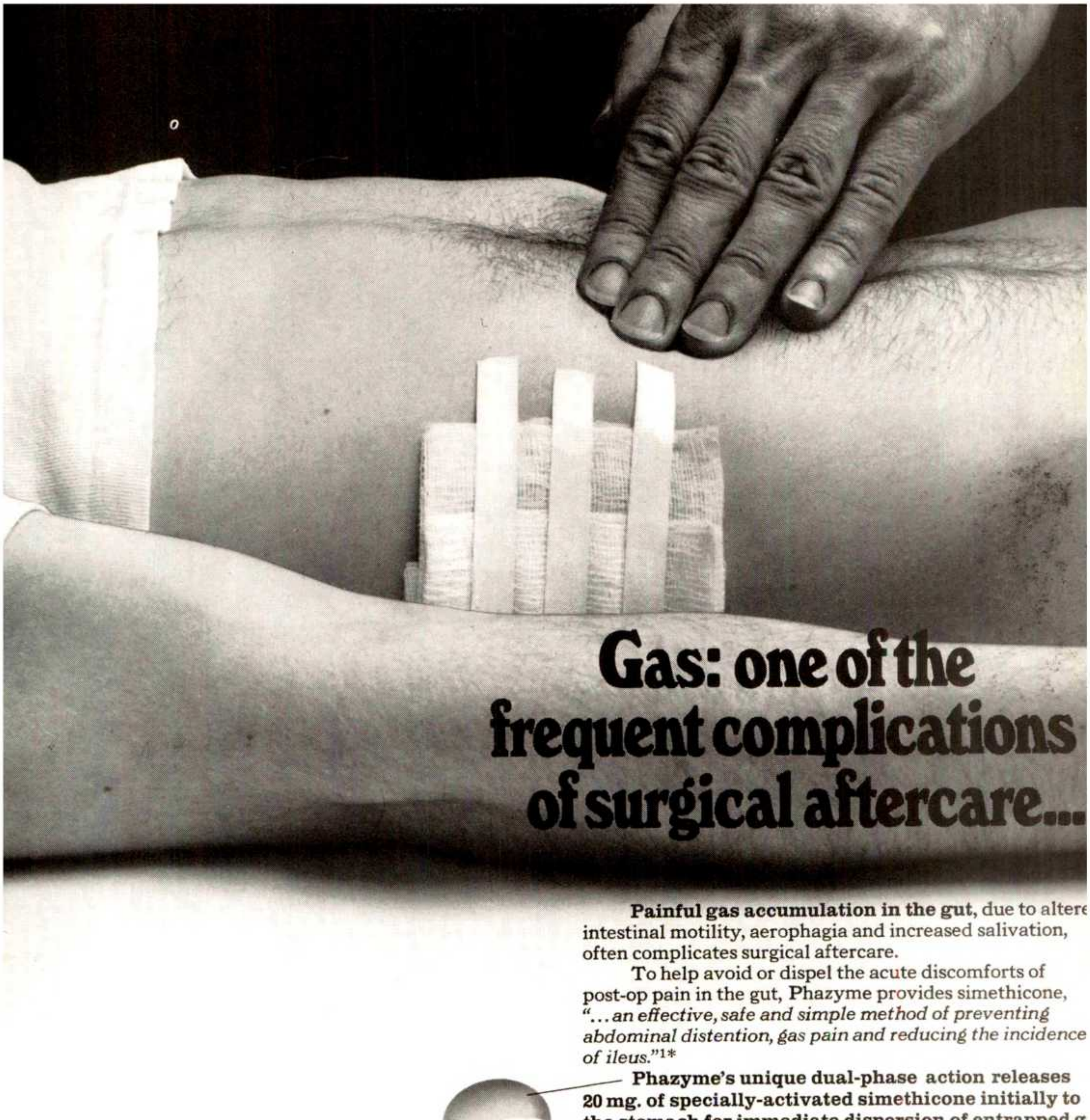

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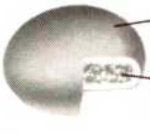

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1. Gibstein, A., *et al.*: Prevention of postoperative abdominal distention and discomfort with simethicone, *Obstet. Gynecol.* 38:386, Sept. 1971.

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Contraindications: pHisoHex should not be used on burned or denuded skin. It should not be used as an occlusive dressing, wet pack, or lotion. It should not be used routinely for prophylactic total body bathing. It should not be used as a vaginal pack or tampon, or on any mucous membranes. pHisoHex should not be used on persons with sensitivity to any of its components. It should not be used on persons who have demonstrated primary light sensitivity to halogenated phenol derivatives because of the possibility of cross-sensitivity to hexachlorophene.

Warnings: RINSE THOROUGHLY AFTER USE, especially from sensitive areas such as the scrotum and perineum.

Infants, especially premature infants or those with dermatoses, are particularly susceptible to hexachlorophene absorption. Systemic toxicity may be manifested by signs of stimulation (irritation) of the central nervous system, sometimes with convulsions. Vacuolization has been reported, with a symmetrical, rostrocaudal distribution in the brainstem reticular formation of premature infants of low birth weight, especially those with skin rashes and wounds, who were washed with 3% hexachlorophene. However, the clinical correlates of such vacuolization have not been established since these infants also had critical clinical conditions or pathologic findings of independent etiology. Some recent opinions express particular concern with respect to the use of pHisoHex on premature infants. Although the scientific picture is still incomplete, pHisoHex should not be used on premature infants unless, in the judgment of the prescribing physician, its use is required by the unique circumstances of an individual case.

When preparations containing hexachlorophene are left in contact with burned or denuded skin or mucous membranes, sufficient hexachlorophene may be absorbed to cause toxic symptoms.

PHISOHEX SHOULD BE DISCONTINUED PROMPTLY IF SIGNS OR SYMPTOMS OF CEREBRAL IRRITABILITY OCCUR. Experimental and clinical evidence indicates that hexachlorophene toxicity is reversible.

In a small number of reported cases, fatal intoxications from hexachlorophene have occurred. These cases include misuse of 3% hexachlorophene on burned skin, or exposure to a powder accidentally containing approximately 6.5% hexachlorophene.

Examinations of brain tissue in some of these cases revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3% hexachlorophene.

pHisoHex is intended for *external use only*. If swallowed, pHisoHex is harmful, especially to infants and children. pHisoHex should not be poured into measuring cups, medicine bottles, or similar containers since it may be mistaken for baby formula or other medications.

Precaution: pHisoHex suds that get into the eyes accidentally during washing should be rinsed out promptly and thoroughly.

Adverse Reactions: Dermatitis and photosensitivity. Sensitivity to hexachlorophene is rare; however, persons who have developed photoallergy to similar compounds also may become sensitive to hexachlorophene.

In persons with highly sensitive skin, the use of pHisoHex may at times produce a reaction characterized by redness and/or mild scaling or dryness, especially when it is combined with such mechanical factors as excessive rubbing or exposure to heat or cold.

Treatment of Accidental Ingestion: The accidental ingestion of pHisoHex in amounts from 1 to 4 oz. has caused anorexia, vomiting, abdominal cramps, diarrhea, dehydration, convulsions, hypotension and shock, and in several reported instances, fatalities. The stomach should be evacuated by emesis or lavage followed by 2 oz. of olive oil or vegetable oil and then by a saline cathartic with symptomatic and supportive treatment as indicated. See package insert or PDR for details.

How Supplied: pHisoHex is available in unbreakable plastic squeeze bottles of 5 ounces, 1 pint, plastic bottles of 1 gallon, and ¼ oz. (8 ml.) unit packets, boxes of 50. pHisoHex should not be dispensed from, or stored in, containers with ordinary metal parts.

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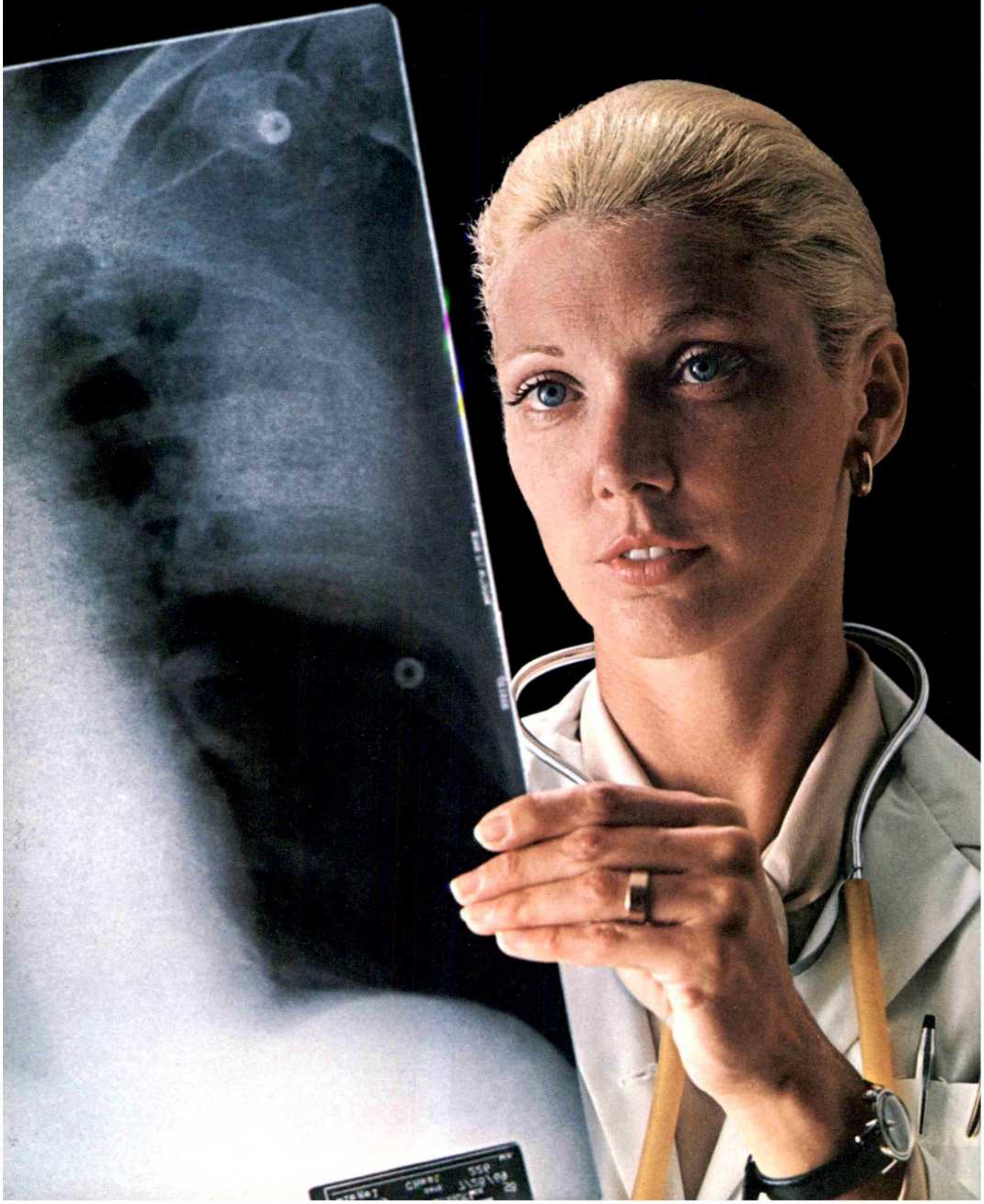
In serious respiratory tract infections*

*due to susceptible microorganisms



ANCEF® IV meets the challenge

- **With 93% efficacy in respiratory tract infections.**
  In clinical trials, 'Ancef' produced good or excellent responses* in 93% of 377 patients with respiratory tract infections due to susceptible organisms (See Indications section of brief summary for list of organisms).
- **With high and prolonged serum levels.**
  Following single 1 gram IV injections in healthy adult volunteers, 'Ancef' produced average peak serum levels of 190.0 mcg/ml. At four hours, levels of 16.5 mcg/ml were still present.
- **With a low risk of phlebitis at the IV injection site.**
  Of 273 patients receiving 'Ancef' intravenously, 6 patients or 2.2% reported phlebitis at the injection site. These data were derived from pre-marketing clinical studies in small populations. While further clinical experience may reveal a greater incidence of adverse effects, it should be noted that the incidence of known phlebitis has not increased with over a year's clinical experience since introduction.
- **With no reported nephrotoxicity.**
  (Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed without evidence of renal or hepatic impairment.)
- **With the flexibility of IV or IM administration.**

Adverse Reactions

Adverse reactions reported in clinical trials included pain on injection, rash, G.I. symptoms, pruritus, and phlebitis. For a complete list of adverse reactions reported with 'Ancef' therapy, please see next page.

Warning: In penicillin-allergic patients, cephalosporins should be used with great caution because of evidence of partial cross-allergenicity.

*(Excellent response: Initial improvement at 1-3 days with maximum improvement between 3-7 days. Good response: Initial improvement at 2-4 days with maximum improvement between 4-10 days. Results collected from identical clinical protocols.)

See next page for a brief summary of the prescribing information.

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

DESCRIPTION

Ancef® (sterile cefazolin sodium, SK&F) is a semi-synthetic cephalosporin for parenteral administration. It is the sodium salt of 3-{[(5-methyl-1, 3, 4-thiadiazol-2-yl) thio] methyl}-8-oxo-7-[2-(1H-tetrazol-1-yl) acetamido]-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid. The sodium content is 46 mg. per gram of cefazolin.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the bactericidal action of cephalosporins results from inhibition of cell wall synthesis. 'Ancef' is active against the following organisms *in vitro:*

Staphylococcus aureus (penicillin-sensitive and penicillin-resistant).

Group A beta-hemolytic streptococci and other strains of streptococci (many strains of enterococci are resistant)

Streptococcus pneumoniae (formerly *D. pneumoniae*)
Escherichia coli
Proteus mirabilis
Klebsiella species
Enterobacter aerogenes
Hemophilus influenzae

Most strains of *Enterobacter cloacae* and indole positive Proteus (*P. vulgaris, P. morgani, P. rettgeri*) are resistant. Methicillin-resistant staphylococci, serratia, pseudomonas, mima, herellea species are almost uniformly resistant to cefazolin.

INDICATIONS

Ancef (sterile cefazolin sodium, SK&F) is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Klebsiella* species, *Hemophilus influenzae, Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Ancef' is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of 'Ancef' in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli, Proteus mirabilis, Klebsiella* species, and some strains of enterobacter and enterococci.

Skin and soft-tissue infections due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci.

Bone and joint infections due to *Staphylococcus aureus.*

Septicemia due to *Streptococcus pneumoniae* (formerly *D. pneumoniae*), *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), *Proteus mirabilis, Escherichia coli,* and *Klebsiella* species.

Endocarditis due to *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci.

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to 'Ancef'.

CONTRAINDICATIONS

'Ancef' is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUG CLASSES (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics, including Ancef (sterile cefazolin sodium, SK&F) cautiously and then only when absolutely necessary. Serious anaphylactoid reactions require immediate emergency treatment with epinephrine. Oxygen, intravenous steroids, and airway management, including intubation, should also be administered as indicated.

Usage in Pregnancy: Safety of this product for use during pregnancy has not been established.

Usage in Infants: Safety for use in prematures and infants under 1 month of age has not been established.

PRECAUTIONS

Prolonged use of cefazolin sodium may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential.

When 'Ancef' is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions). A false positive reaction for glucose in the urine of patients on 'Ancef' has occurred with Clinitest® tablets solution.

ADVERSE REACTIONS

The following reactions have been reported:

Hypersensitivity: Drug fever, skin rash, vulvar pruritus, and eosinophilia have occurred.

Blood: Neutropenia, leukopenia, thrombocythemia and positive direct and indirect Coombs tests have occurred.

Hepatic and Renal: Transient rise in SGOT, SGPT, BUN and alkaline phosphatase levels has been observed.

Gastrointestinal: Nausea, anorexia, vomiting, diarrhea, oral candidiasis (oral thrush) have been reported.

Other: Pain at site of injection after intramuscular administration has occurred, some with induration. Phlebitis at site of injection has been noted.

DOSAGE AND ADMINISTRATION

'Ancef' may be administered intramuscularly or intravenously after reconstitution.

Dosage

In adults, usual dosage for pneumococcal pneumonia is 500 mg. every 12 hours. In acute, uncomplicated urinary tract infections, usual dosage is 1 gram every 12 hours. In mild infections caused by susceptible gram+ cocci, usual dosage is 250 to 500 mg. every 8 hours. In moderate to severe infections, usual dosage is 500 mg. to 1 gram every 6 to 8 hours. 'Ancef' has been administered in dosages of 6 grams per day in serious infections such as endocarditis.

'Ancef' may be used in patients with reduced renal function with the following dosage adjustments: Patients with a creatinine clearance of 55 ml./min. or greater or a serum creatinine of 1.5 mg. % or less can be given full doses. Patients with creatinine clearance rates of 35 to 54 ml./min. or serum creatinine of 1.6 to 3.0 mg. % can also be given full doses, but dosage should be restricted to at least 8-hour intervals. Patients with creatinine clearance rates of 11 to 34 ml./min. or serum creatinine of 3.1 to 4.5 mg. % should be given 1/2 the usual dose every 12 hours. Patients with creatinine clearance rates of 10 ml./min. or less or serum creatinine of 4.6 mg. % or greater should be given 1/2 the usual dose every 18 to 24 hours. All reduced dosage recommendations apply after an initial loading dose appropriate to the severity of the infection.

In children, a total daily dosage of 25 to 50 mg. per kg. (approximately 10 to 20 mg. per pound) of body weight, divided into three or four equal doses, is effective for most mild to moderately severe infections. Total daily dosage may be increased to 100 mg. per kg. (45 mg. per pound) of body weight for severe infections. Since safety for use in premature infants and in infants under one month has not been established, the use of 'Ancef' in these patients is not recommended.

For additional information on dosage and administration, see package literature or contact your SK&F Representative.

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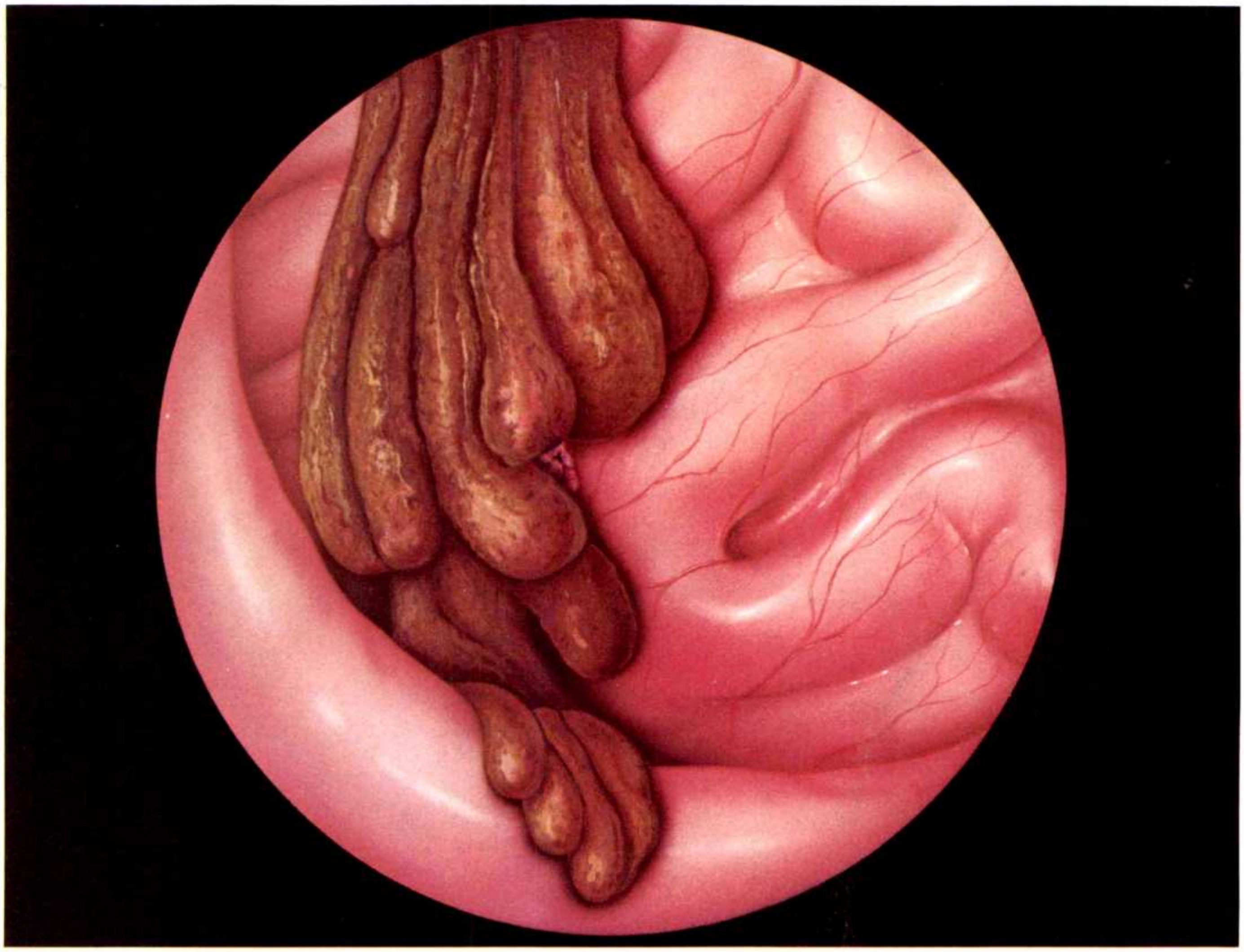

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First Rib Fracture:

A Hallmark of Severe Trauma

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First rib fractures occurred in 55 patients. This injury is a harbinger of major trauma with 35 patients suffering a major chest injury, and abdominal and cardiac injuries occurring in 18 and eight patients respectively. The mortality associated with this injury was high (36.3%). Neurologic lesions accounted for the majority of deaths, however, unrecognized abdominal injuries and pulmonary complications were significant causes of mortality. Brachial plexus injury (5) and Horner's syndrome (3) occurred in survivors. Three patients had an associated injury of the subclavian artery, and the importance of this association is stressed. One late-developing post-traumatic thoracic outlet syndrome occurred. A fracture of the first rib is a hallmark of severe trauma; its presence should alert the clinician to: 1) generalized massive trauma with abdominal, chest, and cardiac injuries; 2) local injury to the subclavian artery and brachial plexus and; 3) necessity of long-term followup for late-developing sequelae.

THE TRAUMA VICTIM with multi-system injuries is one of the most perplexing and difficult patients to manage. Evaluation is especially difficult if there is an associated neurologic injury. The subsequent delay in diagnosis and treatment is a major cause of mortality due to blunt abdominal or chest trauma. [2,3,9,16]

The importance of the radiologic evaluation of accident victims has been stressed by several authors and a number of radiographic signs helpful in assessing the extent of injury have been recognized. On a plain abdominal film, free air, displacement of gas-containing structures, obliteration of the psoas shadow, and the like, suggest visceral injury, while the fracture of certain bony structures indicate the possibility of internal injuries. For example, a fracture of the left eleventh rib should strongly suggest the possibility of a ruptured spleen while myocardial contusion commonly accompanies a sternal fracture.

In evaluating patients with multiple-system injuries we have noted a valuable sign indicative of severe trauma; *i.e.* fracture of the first rib. The anatomy of the first rib is such that it is protected from the minor insults that often break other ribs. Therefore, when a fracture of this bone occurs it should alert the physician to be highly suspicious of other associated injuries regardless of the initial appearance of the patient.

Patient Population

Fifty-five patients with a fracture of the first rib have been treated at the University of Kentucky Medical Center and its affiliated hospitals and the Bexar County Hospital in San Antonio, Texas, in the past ten years. There were 41 males and 14 females with an average age of 33 years. The youngest patient was eight and the oldest 71.

The overwhelming majority (50/55) of these injuries occurred in vehicle accidents. Two patients were pedestrians struck by automobiles, one was injured in a

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TABLE 1. *Associated Injuries With First Rib Fracture (55 Patients)*

Injury	No.	Per cent
Chest	35	64
Abdominal	18	33
Cardiac	8	14
Cranial	29	53
Other fracture	41	75
Other rib fracture	43	78

TABLE 2. *Chest Injuries With First Rib Fracture* (35 Patients)*

Injury	No.
Unilateral pneumothorax	20
Bilateral pneumothorax	7
Hemothorax	14
Pulmonary contusion	22
Flail chest	7

*Many patients had multiple injuries.

mining accident, one in a fall, and the other in a lumbering accident. Most of those injured while in an automobile apparently hit the steering wheel or dashboard. The charts of all patients were reviewed for the occurrence of associated injuries, treatment, and eventual outcome.

Table 1 shows the occurrence of associated injuries in patients with a first rib fracture.

Chest Injuries

Thirty-five of the 55 patients had a major chest injury defined as a pneumothorax, hemothorax, pulmonary contusion, or flail chest (Table 2). Twenty patients had a unilateral pneumothorax while seven had bilateral pneumothoraces. Hemothorax was present in 14 patients and was bilateral in four cases. Twenty-two patients had radiographic evidence of pulmonary contusion. Seven patients had a flail chest.

The treatment of these chest injuries varied somewhat depending on the clinical setting. One patient with a small unilateral pneumothorax was treated with aspiration, but the remainder underwent a tube thoracostomy to allow re-expansion of the collapsed lung. Many had a sizable collection of blood which was drained as well.

One patient with a flail segment was treated with a traction device and the other six by volume ventilation. Thirteen patients (23.6% of the total group) required ventilatory assistance at some point in their management.

The treatment of pulmonary contusion was initially fluid restriction and ventilatory assistance as needed for hypoxia. Recently we have undertaken a more aggressive approach[17,19] using intravenous furosemide, strict fluid limitation, colloid for volume replacement, and vigorous pulmonary care in an attempt to diminish the development of pulmonary contusion and obviate the need for mechanical ventilation.

The severity of the thoracic injury in patients with a first rib fracture is reflected by the hypoxia detected by arterial blood gases. Forty-one patients had an initial determination of arterial blood gases shortly after injury and only 13 had a pO_2 of greater than 80 mm Hg. Eighteen were between 60 and 70 mm Hg at some point in their post-injury phase, while ten persons had an arterial oxygen tension of less than 60 mm Hg.

Abdominal injuries

Eighteen patients (33%) required an explorator laparotomy because of associated intra-abdomina trauma (Table 3). Multiple intra-abdominal injuries wer common. Eleven patients underwent splenectomy, thre had liver lacerations, two had renal injuries, three a intestinal injury and two a ruptured bladder. There wa one negative exploratory laparotomy.

Ten of the 16 patients who required abdominal opera tions had associated neurologic injuries with an altere level of consciousness which made evaluation of thei abdomen difficult on clinical grounds. Diagnosis of ab dominal injury was often strengthened by positiv peritoneal lavage or falling hematocrit; however exploratory laparotomy was occasionally undertake only on strong clinical suspicion.[2] The presence of first rib fracture in these patients was another indicatio that they had indeed received massive trauma and mer ited careful evaluation.

Cardiac Injuries

Eight patients were felt to have cardiac injuries sec ondary to blunt chest trauma. Two patients wit hemopericardium were treated with pericardiocentesis Neither of these patients required further interventio for their cardiac problems. An additional six person were felt to have myocardial contusion as demonstrate by serial changes in their electrocardiogram. Inversio of the T-wave with ST segment depression was seen a some stage in each of the patients. One ECG had re turned to normal within four days while changes in th others persisted two to three weeks. The true incidenc of cardiac contusion may be higher than was actuall diagnosed since several patients did not have an ECG No cardiac injuries were encountered that require operative intervention.

TABLE 3. *Associated Abdominal Injuries* (18 Patients)*

Injury	No.
Ruptured spleen	11
Liver injury	3
Intestinal injury	3
Pancreatic injury	3
Ruptured bladder	2
Renal injury	2
Negative exploration	1

*Many patients had multiple injuries.

Other Associated Injuries

Major injuries associated with first rib fracture were not limited to the thoracoabdominal area. Twenty-nine patients suffered neurologic damage with the majority having a loss of consciousness. The addition of this insult further clouds an already difficult evaluation.

Three-fourths of patients with first rib fracture had an associated fracture of another bone (other than another rib). Long bone fractures of the upper and lower extremities, often multiple, were the most common with ten patients having a pelvic fracture. Forty-three persons had fractures of other ribs. These multiple rib fractures undoubtedly contributed directly to the high number of patients with intra-thoracic injuries.

Mortality

There were 20 deaths in 55 patients with first rib fractures for a mortality of 36.3% (Table 4). Although most patients had combined, multi-system trauma, the leading cause of death was head injury. The combination of a major chest injury with hypoxia and a neurologic lesion was a lethal combination.

Fourteen of the 20 patients who died had a neurologic injury. Eight of these had associated chest trauma and despite ventilatory assistance, this combination of injuries was often difficult to overcome. Three patients also had an unrecognized abdominal injury and in each it contributed to the patient's death. A delayed rupture of the spleen in a man recovering from a head injury produced one death, while another died of sepsis as a result of a mesenteric vascular injury that went undiagnosed with resultant infarction of the colon.

In three patients the deaths were primarily attributable to pulmonary complications. The oldest patient (age 71) suffered a bilateral pulmonary contusion and died of this injury as did one younger patient. A 60-year-old man underwent splenectomy and repair of his fractured femur and then required postoperative treatment on a volume ventilation for his flail chest. Despite a good initial response to therapy, he developed a bilateral pneumonia requiring a prolonged course of ventilatory assistance and eventually died of a suspected pulmonary embolus on his 28th hospital day.

Three other deaths occurred in young men. One died on the operating table from a bursting injury to the liver and another on the third post-injury day from a complication which was diagnosed as fat embolism syndrome. Intra-abdominal sepsis accounted for a third death.

TABLE 4. *Cause of Death*

Neurologic Injury	14	
With chest injury (8)		
With unrecognized abdominal injury (3)		
Primary Pulmonary	3	
Bilateral pulmonary contusion (2)		
Flail chest, ruptured spleen, fractured femur (1)		
Sepsis-Abdominal Injury	1	
Bursting Liver Injury	1	
Fat Embolism Syndrome	1	
Total	20/55	(36.3%)

TABLE 5. *Associated Local Injuries (12)*

Brachial plexus injury	5
Horner's syndrome	3
Arterial injury	3
Thoracic outlet syndrome	1

Local Injuries With First Rib Fracture

Local injuries secondary to fracture of the first rib are shown in Table 5. Brachial plexus injuries occurred most commonly, with three transient and two permanent injuries occurring. Three patients had Horner's syndrome; in two it cleared completely while one patient had a residual ptosis. Arterial injuries to the subclavian artery occurred in three patients. Two patients had large hematomas which signaled the arterial injury while another had radial pulse diminution. Three other patients had first rib fracture with a fractured clavicle and developed sizeable hematomas. Arteriograms were negative in each and they were observed without obvious sequelae. One patient presented three years following a first rib fracture with a thoracic outlet syndrome which appeared secondary to callus formation in the healed fracture. He improved with resection of the first rib.

Discussion

Isolated fracture of the first rib without antecedant injury has been reported.[1,5,13] Alderson[1] noted 73 cases of first rib fracture as an incidental finding in 77,607 chest films, and attributed their occurrence to "stress fracture." Generally, however, it is conceded that a blow of major proportions is needed to produce a first rib fracture. Hinton and Steiner[10] noted first rib fractures occurred in 2.7% of their 807 cases of rib fractures reported in 1940. Conn and associates[6] noted 9.2% of their 532 patients with non-penetrating chest trauma had a fracture of the first rib. The incidence appears to be increasing in recent years due to a greater frequency of high-speed automobile accidents with resultant massive trauma.

The high percentage of associated injuries indicates that persons who suffer a first rib fracture have sustained a major injury. Breslin,[4] in 1937, listed abscess around the clavicle, rupture of the apex of the lung, empyema, pleurisy, hemorrhage and delayed nerve symptoms due to compression from callus as complications of first rib fracture. He also cited a case of subclavian artery injury due to a right first rib fracture. Holmes and Netterville[11] noted that five of their 16 patients with first rib fracture had major chest injuries, three had neurologic damage, and 13 of 16 had other major fractures. In addition, one patient developed a traumatic tracheo-esophageal fistula and another had an aortic arch aneurysm. However, only one patient had an intra-abdominal injury, which is significantly lower than that seen in our patients.

The severity of the trauma inflicted on this group of patients is reflected in the 36.3% mortality rate. Several patients sustained a massive head injury and may have been initially unsalvageable from a neurologic point of view. However, other remediable injuries occurred with frequency and the clinician caring for accident victims must be alert for such problems. In three of our patients abdominal injuries were initially missed and directly contributed to deaths. Missed abdominal injury continues to be a significant cause of mortality following automobile accidents. Gertner et al. [9] reviewed the experience at the Baltimore City Hospitals with deaths following motor injuries due to blunt abdominal trauma and found 32 of 33 fatalities arrived at the hospital alive. They concluded that 50% of these cases had a failure to make either the correct diagnosis or institute proper treatment. At our own institution[16] the delay in recognition of abdominal injuries which often occurred in patients referred from outlying hospitals was an influential factor in mortality from blunt abdominal trauma. While techniques such as diagnostic peritoneal lavage have aided in establishing a diagnosis in massively injured patients, exploratory laparotomy often has been performed on the strong clinical suspicion that such a lesion exists. Those patients with a first rib fracture exemplify such trauma victims.

While a major pulmonary injury may be more easily diagnosed by physical examination with radiological assistance than is an abdominal injury, the presence of a first rib fracture demands careful evaluation for thoracic injuries. Cardiac injuries are frequently missed because they are not considered and appropriate ECG and enzyme studies not obtained.

Major vascular injuries in association with first rib fractures are being recognized with increasing frequency. Galbraight et al. [8] reported a subclavian artery laceration with a first rib fracture and stressed the importance of vascular injuries with this fracture. Sturm and associates[18] treated five patients with rupture of the subclavian artery due to blunt trauma. Three of the patients had a first rib fracture. They recommended arteriography in all patients with fracture of the first three ribs because of the frequent association of subclavian artery injuries. Previously, Fisher and Rienhoff[7] reported a subclavian artery laceration secondary to a first rib fracture. Our experience added to these indicates this association is not rare, and a first rib fracture should alert the clinician to beware of major vascular injury.

In addition to its usefulness as an indication of severe trauma, a fracture of the first rib may produce injuries itself. The report of Holmes and Netterville[11] is the most thorough in outlining this problem. They reported patients with a traumatic tracheoesophageal fistula, aortic arch aneurysm, brachial plexus injury, and Horner's syndrome following first rib fracture. One other patien was found at autopsy to have died from congestive hear failure secondary to bilateral subclavian vein obstruction produced by callus formation due to bilateral firs rib fracture. This death occurred several months post-injury. In our series several patients with Horner's syndrome[12] and brachial plexus injury occurred following a first rib fracture. Additionally, one patient had a post-traumatic thoracic outlet syndrome which was detected three years after first rib fracture. Mulder[14] previously reported seven cases of post-traumatic thoracic outle syndrome with two of these following a first rib fracture These sequelae and the more serious ones reported by others[4,11] may not be initially apparent, therefore, a fracture of the first rib should necessitate a long-term followup to detect late-occurring sequelae.

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Effectiveness of Peritoneal Lavage in Blunt Abdominal Trauma

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To analyze the effectiveness of peritoneal lavage and to define its limitations in the evaluation of patients who have sustained blunt abdominal trauma, a prospective study of 500 such patients was undertaken by the Trauma Service at the Naval Hospital, San Diego. Utilizing a qualitative colorometric method to evaluate the degree of hemoperitoneum, patients could rapidly be divided into three clinical groups: strongly positive, weakly positive, and negative. Using this method, patients with a strongly positive peritoneal lavage had a 94% incidence of significant intra-abdominal injuries. In 333 patients with a negative lavage, there was no documented incidence of significant intra-abdominal injuries. In the weakly positive lavage group, only 9 patients out of 99 subsequently proved to have significant intra-abdominal injuries. Visceral angiography and abdominal echography were utilized in this group of patients to identify those with significant intra-abdominal injuries. By utilizing this approach, there were only eight unnecessary celiotomies in the total group of 500 patients. It is concluded, therefore, that peritoneal lavage is a safe, rapid, and effective means of evaluating patients who have sustained blunt abdominal trauma.

WITH the increased incidence of highway accidents the surgeon is confronted more often with the responsibility of making a rapid, accurate assessment of intraperitoneal injuries in the patient who has sustained blunt injury to his abdomen. The rapidity and accuracy of this initial assessment becomes of utmost importance, since the associated morbidity and mortality is directly related both to the magnitude of the injury and to delays in instituting appropriate therapy. Physical examination in this group of patients is often misleading and routine laboratory work and x-rays are seldom helpful. Surgeons in several large institutions[1,4,8,10,12,13,15] have, therefore, begun to utilize peritoneal lavage to aid them in deciding whether immediate celiotomy is necessary or whether the treatment of associated injuries can be safely undertaken.

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To analyze not only the effectiveness of this procedure but also to define its limitations in the evaluation of the patient who has sustained blunt abdominal injury, a prospective study of 500 such patients was undertaken by the Trauma Service at the Naval Hospital San Diego.

Materials and Methods

From April, 1972 through January, 1974, 500 consecutive patients with blunt abdominal trauma were evaluated by the Trauma Service and underwent peritoneal lavage. This included all patients who had sustained sufficient force to have caused intra-abdominal injury regardless of abdominal findings. The only contraindications to lavage were: 1)multiple previous abdominal operations; 2) a pregnant patient; or 3) an unstable patient requiring immediate surgery.

All patients were classified into four clinical groups by the senior surgical resident on the basis of physical findings: 1) surgical, 2) equivocal, 3) non-surgical, and 4) unconscious. After initial resuscitation, they underwent peritoneal lavage using the technique described by Root[13] and modified by Perry.[11] Adult patients were lavaged with 1

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TABLE 1. *Correlation of Peritoneal Lavage Results and Initial Physical Examinations With the Incidence of Significant Intraperitoneal Injurie*

Clinical Evaluation	Strongly Positive No. Patient	Strongly Positive No. Injuries	Strongly Positive %	Weakly Positive No. Patient	Weakly Positive No. Injuries	Weakly Positive %	Negative No. Patient	Negative No. Injuries	Negative %	Total Patients	Total Injuries	Total %
Surgical	39	35	90	6	2	33	17	0	0	62	37	60
Equivocal	12	12	100	43	4	9	101	0	0	156	16	10
Non-surgical	12	12	100	43	3	7	198	0	0	253	15	6
Unconscious	5	5	100	7	0	0	17	0	0	29	5	17
Total	68	64	94	99	9	9	333	0	0	500	73	15

Liter of normal saline while 20 cc/kg saline was used in children. When the infusion was completed, the empty bottle was placed on the floor and allowed to drain by gravity. The fluid was interpreted by the qualitative colorimetric method originally described by Olsen.[10] Using this technique, patients were divided rapidly into three groups: negative, weakly positive, and strongly positive.

Patients with a strongly positive lavage underwent immediate celiotomy. Those with a negative lavage were admitted for treatment of associated injuries or for observation for 24 hours. Those with a weakly positive lavage underwent further diagnostic evaluation to determine if there was a significant intra-abdominal injury. This included abdominal echography in all patients and visceral arteriography in patients with positive echograms. All patients with a positive arteriogram underwent celiotomy. Aliquots of lavage fluid were sent to the laboratory for WBC count, amylase, gram stain, and culture and sensitivity.

Results

Table 1 summarizes the data. In 500 lavages there were 68 strongly positive, 99 weakly positive, and 333 negative lavages. Of the strongly positive group, 64 had a significant injury at celiotomy for a 94% accuracy. In the weakly positive group, only 9 of 99 had a significant injury (9%). Considering all patients with hemoperitoneum only 73 of 167 (44%) had a significant injury. In the negative group of 333 there were no significant injuries.

TABLE 2. *Significant Intra-abdominal Injuries*

	Strongly Positive Lavage Group	Weakly Positive Lavage Group	Total
Spleen	45	4	49
Liver	15	2	17
Kidney	3	3	6
Mesentery	4	1	5
Pancreas	3	1	4
Intestine	3	0	3
Bladder	2	0	2
Diaphragm	0	1	1
Vascular (Venous)	3	1	4
Omentum	1	0	1
Other	1	0	1
	80	13	93

The inaccuracy of the initial physical examination i indicated in Table 1. Of 62 patients that were considered t have a surgical abdomen on initial evaluation and wh would have undergone a celiotomy only 37 (60%) had significant intra-abdominal injury. Therefore, 25 patient (40%) were spared an unnecessary celiotomy. Of the patients felt to have a non-surgical abdomen on initial evaluation, 15 of 253 (6%) were found to have a significant injury In the equivocal group only 16 of 156 (10%) were found t have a significant intra-abdominal injury. Five of 29 (17% of the unconscious patients had significant intra-abdomina pathology. The injuries encountered are listed in Table and as expected solid viscus injury (spleen, liver) was th most common. In the weakly positive group of 99 patient there were 41 normal, 20 abnormal and 2 unsatisfactor echograms. Of the 20 abnormal echograms significant injuries were documented in only three cases. There were n false negative echograms. Of 42 visceral arteriograms i this group, there were 33 normal, 8 abnormal, and on unsatisfactory study. All 8 patients with an abnormal arteriogram underwent celiotomy and five had a significan intra-abdominal injury.

In the 500 patients there were 81 celiotomies. In 8 of thes no significant intra-abdominal injury was demonstrate

TABLE 3. *Summary of Operative Indications and Injuries in the Eight Negative Celiotomies*

Lavage Group	Patient No.	Operative Indication	Operative Findings
Strongly positive	1	Lavage findings	Omental tear
	2		Retroperitoneal hematoma
	3		Minor liver lacerations
	4		None*
Weakly positive	5	Positive splenic arteriogram	None
	6	Positive splenic arteriogram	Minor liver laceration
	7	Positive hepatic arteriogram	Retroperitoneal hematoma
	8	Change in clinical course	None

*Incorrect lavage technique.

TABLE 4. *Lavage WBC Count and Amylase Values*

Lavage Result	*Lavage WBC*		*Lavage Amylase*	
	$<500/\text{mm}^3$	$>500/\text{mm}^3$	<100A.U.%	>100A.U.%
Strongly Positive	5 (5)	12 (12)	20 (19)	3 (3)
Weakly Positive	43 (1)	11 (0)	57 (1)	3 (1)
Negative	175 (1)*	18 (1)*	196 (0)	9 (0)
Total	223 (7)	41 (13)	273 (20)	15 (4)

( ) Denotes the number of patients with a significant injury.

* Renal injury without intraperitoneal trauma.

Four were in the strongly positive group and four were in the weakly positive group (Table 3). Three of the four strongly positive lavages had an insignificant injury (minor liver laceration, omental tear, retroperitoneal hematoma) and one lavage was performed incorrectly. In the weakly positive group, three of the four unnecessary operations were performed because of false positive angiograms. The fourth case was operated on early in the study in spite of a negative arteriogram because of significant physical findings.

There were 264 lavage fluid WBC count and 288 lavage amylase values available for analysis (Table 4). In the group of 223 patients with less than 500 WBC/mm^3 in the lavage fluid, there were six significant intra-peritoneal injuries and one retroperitoneal injury. The six intraperitoneal injuries all had positive lavages. The retroperitoneal injury was a patient with a negative lavage who had hematuria and a positive IVP for a renal injury. There were 41 patients with a lavage WBC count greater than $500/\text{mm}^3$ and only 13 of these had a significant injury. Twelve of these were intraperitoneal injuries and all had strongly positive lavages. The other patient had a renal injury with a negative lavage. Thus, 17 of 18 patients (94%) with an elevated lavage WBC count in the negative lavage group had no intra-abdominal injury. Of the 273 patients with a lavage amylase less than 100 AU%, 20 had a significant injury. All 20 of these were operated on because of strongly or weakly positive lavage. Only four of 15 patients with a lavage amylase greater than 100 AU% had a significant injury and all four had concomitant hemoperitoneum. Nine patients with negative lavages and elevated lavage fluid amylases proved to have no intra-abdominal injury.

In 500 peritoneal lavages there were no major complications. There was a 6% incidence of minor complications including wound separation and wound hematoma.

Discussion

Two of the strongest criticisms of the use of peritoneal lavage as a diagnostic tool in blunt abdominal trauma center around its potential complications and also its extreme sensitivity in diagnosing clinically insignificant hemoperitoneum. Major complications that have been reported with the use of peritoneal lavage have been visceral perforation and hemorrhage secondary to lacerations of major vessels.[15] The incidence of these complications can be minimized by excluding patients with a history of multiple abdominal surgical procedures, the use of countertraction after direct visualization of the linea alba, and insuring that the bladder is emptied. Adherance to these criteria has eliminated any major complications in our 500 patients. Our morbidity rate of 6% consisted only of local wound problems such as hematoma and separation. We feel that the following are absolute contraindications to peritoneal lavage: 1) history of multiple abdominal surgical procedures; 2) pregnancy; and 3) the presence of a full bladder. If a patient has had lower abdominal surgery or a fractured pelvis, the peritoneal lavage can be safely done through an upper midline incision.

It is true that peritoneal lavage is extremely sensitive in determining the presence of blood within the peritoneal cavity. This is graphically demonstrated by the fact that as little as eight drops of blood in a liter of saline will cause a pink discoloration to appear. Indeed, if we had used the presence of any degree of hemoperitoneum alone as an indication for celiotomy our incidence of negative celiotomies would have been 66% rather than our true incidence of 5%. As a result of this oversensitivity of the peritoneal lavage technique, several methods have been recommended to quantitate the degree of hemoperitoneum and to correlate this with clinical significance.[4,10,11,12,15] These include measuring the hematocrit, red blood cell count, and finally the qualitative colorimetric method first described by Olsen.[10] This latter technique has the advantage of allowing the physician at the bedside to quickly place the patient into one of three groups: 1) strongly positive; 2) weakly positive; and 3) negative. We adopted this latter method because of its bedside applicability and because of the fact that in Olsen's series there was a good clinical correlation. Ninety-eight per cent of the patients in his strongly positive group had significant intra-abdominal injuries, while only 32% of the patients in his weakly positive group had significant injuries. When we applied these same criteria for division of our patients, we had a 94% incidence of significant injuries in the strongly positive group and only a 9% incidence in the weakly positive group. We feel that this discrepancy in the weakly positive group is due to the larger percentage (57/99 vs 3/25) of trace lavage in our series. Actually our incidence of significant injuries in the weakly positive group would have been 21% if we had excluded the trace lavage. This group probably represents contamination from abdominal wall bleeding. In both series, the presence of an absolute negative lavage ruled out significant intra-abdominal injuries in 100% of the cases. From this data, it is apparent that the weakly positive lavage group requires further evaluation as less than one third will have significant intra-abdominal injuries. It is

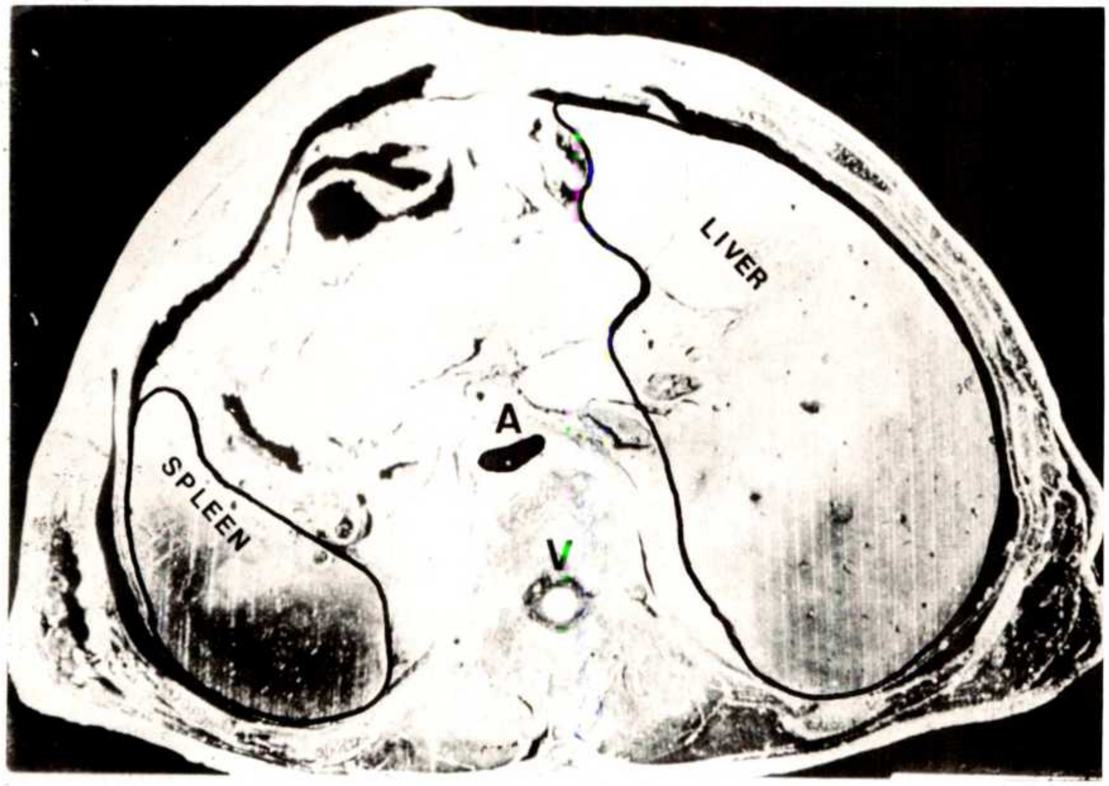

FIG. 1. Cross section of a supine cadaver. Note the medial border of the spleen is smooth and the anterior edge does not extend past the level of the aorta (A). (V) represents the vertebral body.

within this group that the use of echography and abdominal angiography proved to be helpful.

Echography is a rapid, non-invasive technique utilizing ultrasound to define the configuration of both intra-abdominal and retroperitoneal structures.[3] Its use in the area of blunt abdominal trauma is for the most part limited to the diagnosis of splenic injury. Criteria for ruptured spleen by echography center around demonstration of enlargment and irregularity in its contour (Figs. 1-3). In our series, the percentage of false positive echograms (85%) precluded the use of this technique as a criterion for exploratory celiotomy. However, we had no false negative

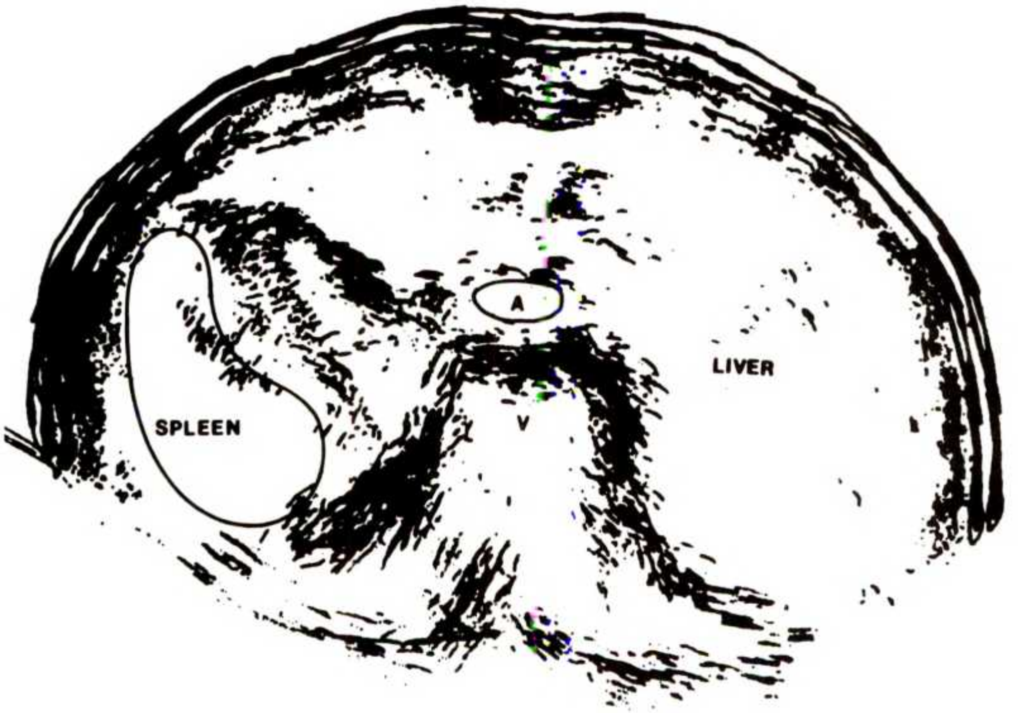

FIG. 2. Normal spleen by echography. Note the smooth medial contour and that the anterior edge is parallel with the aorta (A). (V) represents the vertebral body.

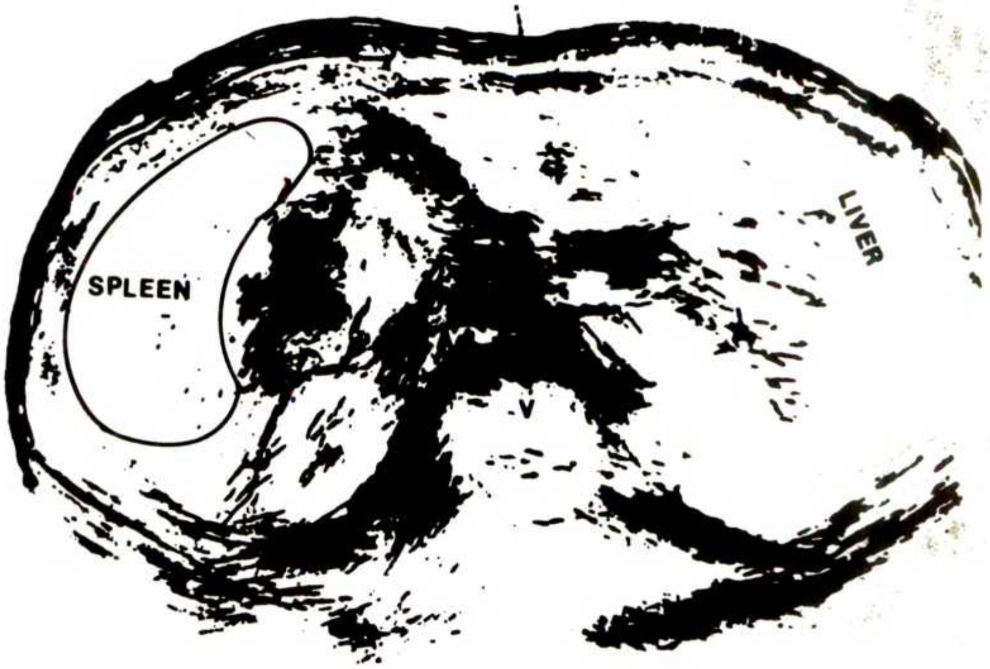

FIG. 3. Ruptured spleen by echography. Note the marked enlargement of the spleen with the anterior edge extending almost to the anterior abdominal wall. (V) represents the vertebral body.

echograms, therefore, the technique may be useful as a rapid non-invasive maneuver in patients with a weakly positive lavage. If the echogram is positive then it is imperative that the patient undergo visceral arteriography. We use flush abdominal aortograms followed by selective celiac studies. By using this technique, hepatic, renal and intestional injuries can be documented in addition to splenic injuries. The criteria commonly used for the diagnosis of splenic injury are:[5,16] 1) puddling of the dye; 2) stretched displaced vessels; 3) avascular areas; 4) early venous filling; and 5) pseudo-aneurysms. Figures 4 and 5 demonstrate several of these abnormalities. By utilizing the combination of echography and arteriography in the group of 99 patients with a weakly positive lavage only 12 of these patients underwent celiotomy. Within this group of 12 patients there were 9 significant intra-abdominal injuries and only 3 negative celiotomies. These 3 patients represented false positive angiograms. Thus, by taking the more aggressive diagnostic approach and the more conservative clinical approach, 87 patients of the 99 with a weakly positive lavage were spared an unnecessary celiotomy. The attending physicians were thus able to rapidly proceed with the care of associated injuries without the fear of overlooking significant intra-abdominal pathology.

It has been suggested that greater than 100 amylase units per cc of clear peritoneal lavage fluid is diagnostic of pancreatic or small bowel injuries in patients sustaining blunt abdominal trauma.[11,12,15] In our series there were nine instances in which the lavage amylase was greater than 100 amylase units % in patients with a negative lavage. None of these patients had a significant intra-peritoneal injury. Of the six patients with hemoperitoneum and an elevated la-

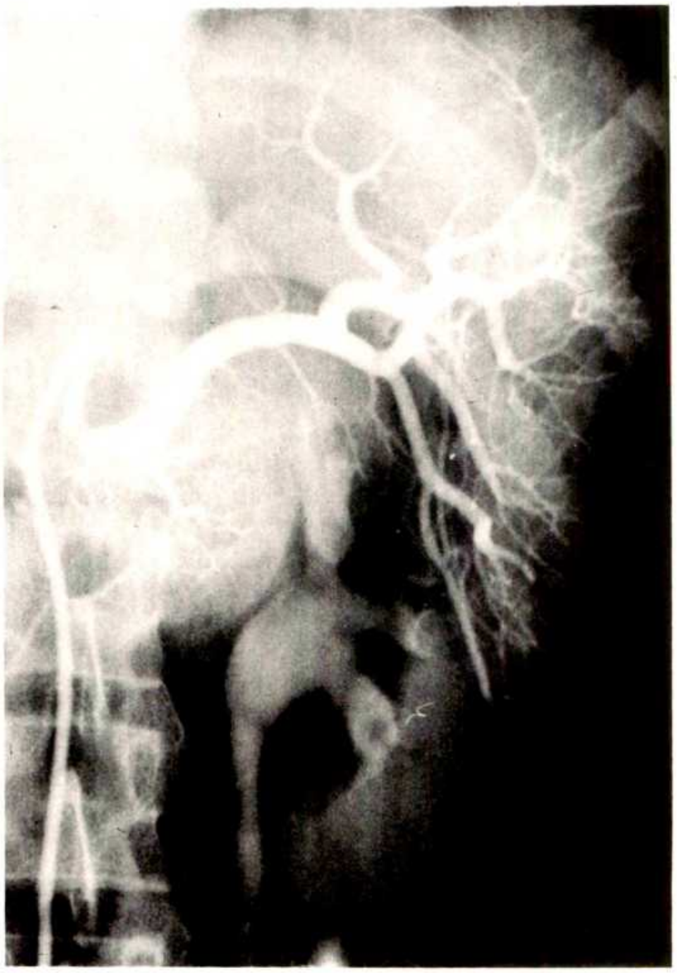

FIG. 4. Ruptured spleen by arteriography (arterial phase). Note stretching of the splenic arteries in the upper pole.

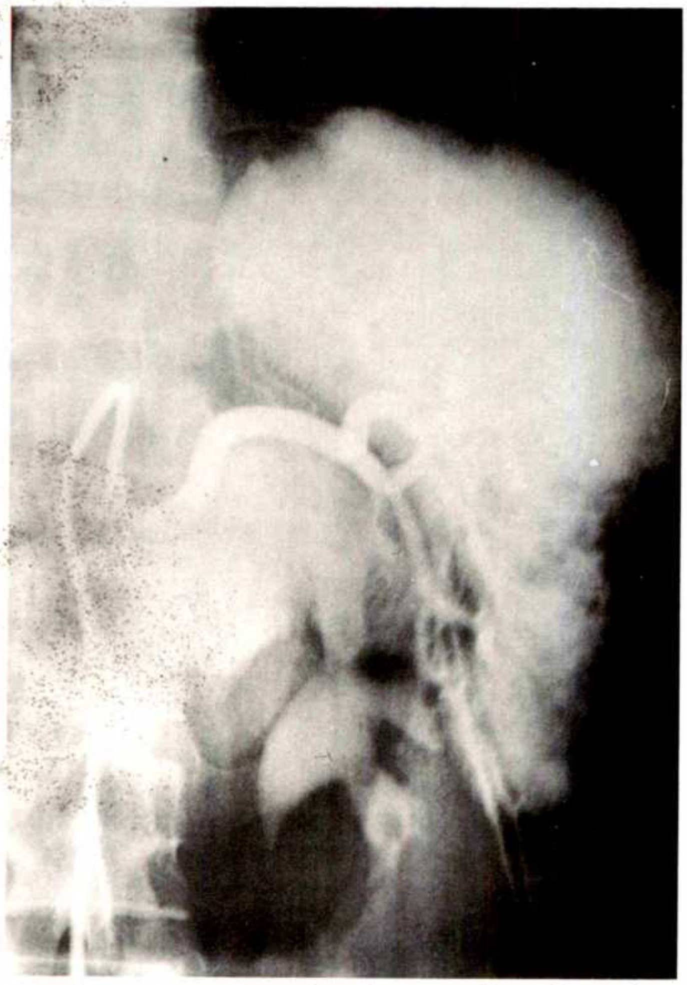

FIG. 5. Ruptured spleen by arteriography (venous phase). Note the large avascular area in the lower pole.

vage amylase, four had significant injuries. Three of these were in the strongly positive group and would have been operated on this basis alone. The fourth patient with a significant injury was in the weakly positive group and had a renal injury requiring nephrectomy. This injury was diagnosed by visceral arteriogram and IVP. We, therefore, feel that an elevated lavage fluid amylase in a clear aspirate is not an indication for celiotomy. It has been recently demonstrated that the level of serum amylase was also a poor predictor of the presence or absence of significant injuries.[9] However, we feel that an elevated lavage amylase and a progressively increasing serum amylase coupled with persistant abdominal findings should be an indication for exploratory celiotomy.

The presence of over 500 white blood cells within the peritoneal lavage fluid has been used as an indication for celiotomy.[11,12,15] In our 18 patients with a clear lavage and an associated white count greater than 500/mm³ only one had a significant injury. This patient had a lacerated kidney that was diagnosed by an IVP performed for gross hematuria. If an elevated lavage fluid white count had been used as an indication for exploration, 17 patients would have undergone unnecessary celiotomy. We thus feel that the presence of white cells within clear peritoneal lavage fluid is not in itself an indication for celiotomy.

This study re-emphasizes the inaccuracy of the initial physical examination in patients with blunt abdominal trauma. Forty per cent of the patients felt to have a surgical abdomen had no intra-abdominal injury. We feel this high incidence of false positive exams is caused by abdominal wall contusions and associated injuries of the chest, spine, and pelvis which produce muscular spasm indistinguishable from the guarding associated with true intraperitoneal injury. It is also evident that there are fewer false negative exams, with the overall incidence in our series being 6%. The negative initial physical examination with significant intra-abdominal injury may be ascribed to the frequency of solid organ injury in blunt abdominal trauma. The hemoperitoneum accompanying this type of injury produces much less peritoneal irritation than intestinal contents. We had several patients with large amounts of blood in their peritoneal cavity with no abnormal physical findings. The high degree of accuracy with peritoneal lavage as contrasted to the relative inaccuracy of the physical examination has led to a marked decrease in overall morbidity in our patients. It is apparent that 40% of the patients with false positive physical examinations were spared an unnecessary laparotomy and there was no delay in managing their associated injuries. Six per cent of patients with initial false negative exams as well as 10% of patients in the equivocal group had a minimal delay in exploration.

The morbidity and mortality of negative laparotomy is frequently underestimated while the complications associated with a missed injury are well-known.[2] A recent report on penetrating trauma had a corrected operative mortality for a negative celiotomy of 1.6% with a morbidity rate of 19–23%.[6] Maynard and Oropeza[7] reported five deaths in 79 negative celiotomies (6.3%) for penetrating injuries. Similar statistics are unavailable for blunt abdominal trauma. However, one would postulate because of the frequently associated multiple injuries that there would be an increased morbidity and mortality.

Although peritoneal lavage is highly accurate in diagnosing intraperitoneal injuries, it is not as accurate with retroperitoneal injuries. Occasionally these injuries may be detected by peritoneal lavage because of the diapedesis of red cells through the posterior parietal peritoneum. There were three major isolated renal injuries in our series without significant intraperitoneal damage which produced a weakly positive lavage. However, this should not be relied on and if a retroperitoneal injury is suspected, an intravenous pyelogram, renal arteriogram, or gastrograffin duodenogram should be performed.

To manage blunt abdominal trauma rapidly and efficiently, we recommend the following protocol. In the emergency room a lavage is performed and if strongly positive, (red and opaque or print cannot be read through the tubing), the patient undergoes immediate celiotomy. If the lavage is negative and there are no associated injuries, the patient is observed for 24 hours. If the lavage is weakly positive, (pink and clear or print can be read through the tubing), the patient undergoes echography and arteriography, if stable. If the arteriogram is positive the patient undergoes celiotomy and if negative the patient is observed 48 hours. Thus, our indications for celiotomy in blunt abdominal trauma are: 1) a strongly positive lavage; 2) a weakly positive lavage with positive arteriogram; and 3) an unstable patient.

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Cricopharyngeal Myotomy:

Treatment of Dysphagia

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Six patients are presented who underwent cricopharyngeus myotomy for dysphagia. The clinical history and cine studies appear to be the most useful assessments in defining patients with dysphagia who may improve after a myotomy. Etiological factors which may precipitate poor coordination of the swallowing mechanism and a relative cricopharyngeus muscle obstruction include neuromuscular disorders, radical oral surgery, central nervous disease, and idiopathic disorders. Although the exact physiology of the cricopharyngeus muscle in health and disease is not as yet delineated, the muscle is being implicated in many problems as the inciting factor of upper esophageal dysphagia. The operation of cricopharyngeus myotomy is a relatively simple procedure and should be done with little morbidity and mortality in properly selected cases.

CRICOPHARYNGEAL MYOTOMY has been reported by many authors over the past decade for the treatment of Zenker's pulson diverticulum.[3,4,6–8,11–14,24,25] Only sporadic reports have been published of cricopharyngeal myotomy for dysphagia, achalasia, or oral and pharyngeal resection where swallowing is impaired.

Valsalva in 1777 is credited with describing the cricopharyngeal muscle and suggested that it was a separate entity from the inferior constrictor muscles. Recently the anatomist and physiologist have begun to work out the function of this muscle.[10,27]

As early as 1926, Jackson[18] implicated the cricopharyngeal muscle as a precipitating factor in the development of Zenker's pulsion diverticulum and advocated dilatation after resection of the diverticulum. Later, in 1946, Lahey[19] concurred with Jackson's opinion and also advised dilatation or resection of the muscle. In 1950, Asherson[2] reported a series of cases of dysphagia and introduced the term "cricopharyngeal achalasia." The similarity between cricopharyngeal achalasia and so called "cardiospasm of the lower esophagus" was suggested. Using cine studies, Dohlman[9] demonstrated dysfunction of the cricopharyngeal muscle in patients with pulsion diverticulum and proceeded to recommend, in 1960, endo-cricopharyngeus myotomy.[8] Since then, many authors have advocated cricopharyngeal myotomy as either the primary treatment of pulsion diverticulum or to compliment resection of the diverticulum.

Ardan[1] in 1961 and later Ellis,[10] demonstrated by manometric studies that patients with pulsion diverticulum show an early closure of the cricopharyngeal muscle before the act of swallowing is completed.

Neuromuscular disorders have been implicated as an etiological factor in dysphagia of the upper esophagus and were reviewed by Belsey[3] in 1966. Kaplan[15] in 1951 reported doing a myotomy on a patient with neuromuscular dysphagia. Ogura[22] observed in 1960 that patients following radical oral and pharyngeal resections often had difficulty in swallowing. The normal swallowing mechanism appeared to be altered and the

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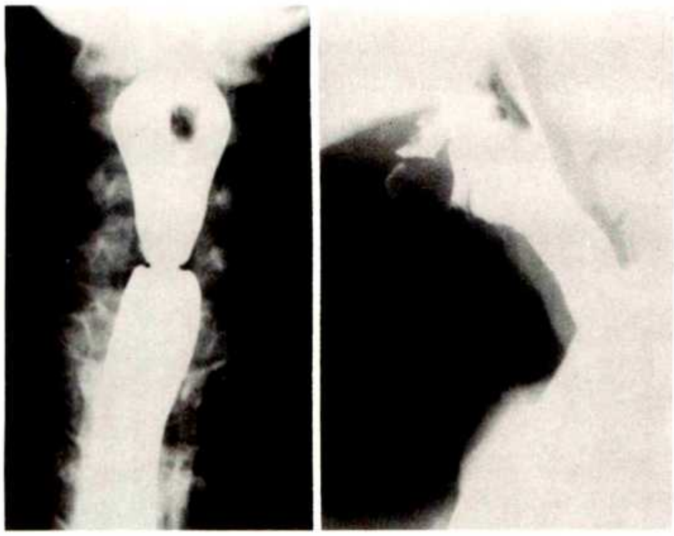

FIG. 1. (Left) Preoperative esophogram demonstrates concentric narrowing of the esophagus at the level of the cricopharyngeus. (Right) The second film shows the area (lateral projection) after surgery.

cricopharyngeus acted as an impediment to the weakened pharyngeal mechanism of propelling the food into the esophagus. Subsequently, Ogura advised cricopharyngeal myotomy routinely in patients undergoing supraglottic pharyngectomies.

We have recently treated six patients diagnosed as having upper esophageal dysphagia secondary to pharyngeal-cricopharyngeus muscle dysfunction and herein report these cases and review of the literature.

Anatomy and Physiology

The cricopharyngeus is now recognized as a true sphincter. It arises from the lateral borders of the cricoid cartilage and runs posterior to the wall of the esophagus without having a median raphe as do the constrictors of the pharynx. Superiorly, the cricopharyngeus muscle is bordered by the inferior constrictor and between the two muscles is where the Zenker's pulsion diverticulum presents. Inferiorly, the cricopharyngeus muscle merges with longitudinal and circular fibers of the upper esophagus.

No one nerve has been delineated to innervate the cricopharyngeus muscle, however, animal experiments and clinical observations suggest that both sympathetic and parasympathetic systems are involved.[21,22] Most authorities believe that the cricopharyngeus muscle derives its primary innervation from the vagus.[10]

Case Reports

Case 1. The patient, a 42-year-old white woman, was admitted first with a chief complaint of food stuck in her throat. Barium swallow showed a bolus of food in the hypopharynx, but she was able to swallow it in the subsequent hour. A followup esophagram (Fig. 1) revealed a spasm of the cricopharyngeus area. Pressure and motility studies were entirely within normal limits.

In retrospect, the patient remembered numerous occasions over the past nine years when she had had difficulty swallowing and had had one previous episode of food sticking in her throat over a prolonged period of time. No neuropathy or myopathy was found on physical examination.

The patient underwent a cricopharyngeus myotomy with a diagnosis of spasm of the cricopharyngeus muscle apparent on cine studies. She was able to eat on the first postoperative day and noted immediate improvement of her swallowing mechanism. She was discharged on the third postoperative day. Followup cine studies (Fig. 1) showed a marked improvement in the upper esophagus. She is now six months post surgery and manifests no apparent dysfunction of her swallowing mechanism.

Comment. The x-rays demonstrate an esophageal "web" which Belsey[3] aptly suggests "defies objective elucidation." Only muscle spasm was noted at surgery without submucosal fibrosis.

Case 2. The patient is a 67-year-old man who gave a history of increasing difficulty in swallowing, especially liquids. He choked when he swallowed and much of his food was coughed out his nose. It was felt that in the past he had suffered a mild CVA with a slight bulbar type palsy. Cine fluoroscopy of the esophagus demonstrated a neuromuscular dysfunction of the pharyngeal area with aspiration into the tracheobronchial tree (Fig. 2). Dilatation of the hypopharynx and holdup at the cricopharyngeus was apparent. It was observed that he had some left vocal cord sluggishness and he had noted a slight change in his voice.

On June 25, 1973, the patient underwent a cricopharyngeal myotomy. On the first postoperative day he noted improvement in his swallowing mechanism and this continued in the ensuing followup. He is presently able to eat both solids and liquids without coughing or apparent dysphagia, 2½ years postop. Followup cine studies reveal that fluid passes much faster into the upper esophagus.

Case 3. The patient is an 85-year-old man who was first seen in 1961 with difficulty in swallowing. He was noted to have a large pharyngeal diverticulum and was taken to surgery where a diverticulectomy was performed. His swallowing improved but an element of dysphagia re-

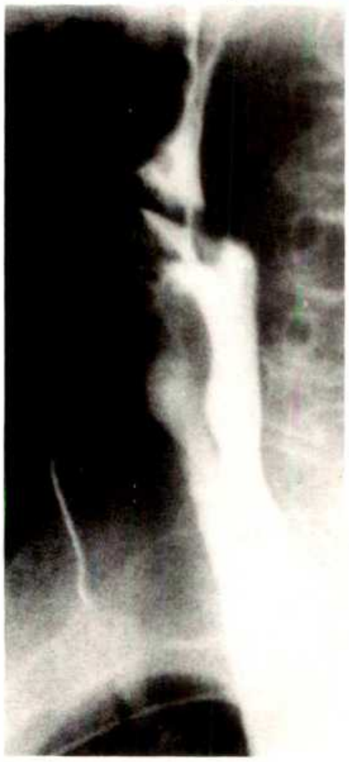

FIG. 2. Cine studies revealed aspiration into the tracheobronchial tree which was not apparent on followup cine studies after cricopharyngeus myotomy.

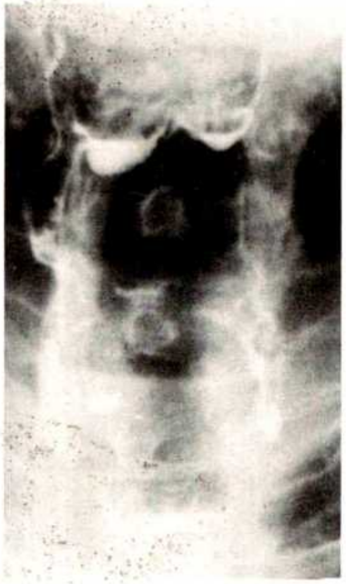

Fig. 3. Barium swallow demonstrated a large esophageal diverticulum 11 years after the original resection of a Zenker's diverticulum.

mained. By late 1971 he observed increasing difficulty in walking and also in swallowing. Workup revealed generalized arteriosclerosis with peripheral neuropathy and barium swallow showed a recurrence of the diverticulum (Fig. 3). Cine studies revealed holdup in the pharyngeal region.

On January 17, 1972, the patient underwent a cricopharyngeal myotomy. The recurrent diverticulum was not removed. Postoperatively the patient denied dysphagia or aspiration.

Comment. Recurrent pharyngeal diverticulum has occasionally been reported. Rather than an inherent weakness in the pharyngeal wall, pharyngeal-cricopharyngeus dysfunction no doubt existed in this patient and resection of the diverticulum alone did not resolve the dysphagia.

Case 4. The patient, a 73-year-old man, was seen first in February, 1971, with a 3–4 year history of increasing swallowing problems. The food appeared to stick in the pharynx and even liquids presented difficulty. Over the past 4–6 months his problem progressed to the point that he was embarrassed to eat at the table because of aspiration and coughing spasms with food being coughed out the nose. He lost 7–8 pounds. It is pertinent that he had ptosis of both eyes repaired two years earlier and a question of an oculopharyngeal syndrome was raised. A neurologist diagnosed amyotrophic lateral sclerosis, especially involving the eyes and the pharynx.

Fluoroscopy revealed incoordination with distention of the pharyngeal recesses, vallecular retention and aspiration into the tracheobronchial tree (Fig. 4). Pressure studies of the cricopharyngeal region were normal.

On February 23, 1971, the patient underwent a cricopharyngeal myotomy. He noted immediate improvement on the following day and was discharged three days postoperatively swallowing both liquids and solids without any difficulty of dysphagia, regurgitation, or coughing problems.

Three months postoperatively, a repeat cine barium swallow showed marked decrease in the hypopharyngeal retention although not completely normal (Fig. 4). Two-and-one-half years postoperatively he has no complaints relative to swallowing.

Comment. Cine studies suggested a marked weakness of the muscles above the cricopharyngeus with a relative obstruction at the cricopharyngeus. A myotomy was suggested to relieve the area of relative obstruction, although pressure studies were normal.

Case 5. The patient is a 63-year-old woman who was diagnosed as having amyotrophic lateral sclerosis in mid-1973 with marked dysarthria and dysphagia. Cine studies showed severe difficulty with the swallowing mechanism involving the tongue and the pharynx. Motility of the esophagus appeared normal. Pressure studies were normal of the cricopharyngeal area. The patient was quite alert mentally and ambulatory, but the dysarthria was sufficiently disabling that she was able to communicate only by writing. She had lost 10–15 pounds because of the difficulty of oral intake.

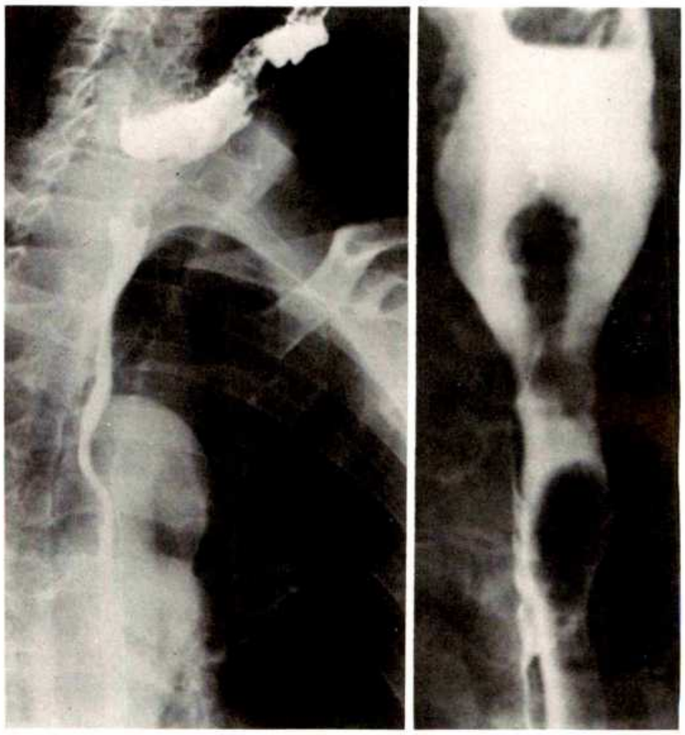

FIG. 4. (Left) Barium swallow demonstrating holdup at the cricopharyngeus area and aspiration: (Right) no apparent holdup postoperatively.

Cricopharyngeus myotomy was performed and she was taking liquids on the first postoperative day and discharged taking a soft diet on the third postoperative day. Although her swallowing did not return to normal both she and her family noticed marked improvement in her ability to take both liquids and solids and weight gain was attained. Only two episodes of aspiration and coughing spells have occurred postop.

Case 6. The patient, a 73-year-old man, was admitted because of progressive chronic obstructive pulmonary disease and pneumonia. He had arteriosclerosis with increasing central nervous system problems. Tracheostomy was required and with this he manifested aspiration and difficulty swallowing. Cine studies were performed and showed relative holdup at the cricopharyngeal area with aspiration into the tracheobronchial tree.

Cricopharyngeus myotomy was performed and postoperatively the patient's swallowing mechanism improved and there was no overt aspiration or egress of fluid from the permanent tracheostomy.

Operative Technique

On the left side, an oblique incision is made at the anterior border of the stenocleidomastoid beginning at the suprasternal notch and carried cephalad to just below the base of the ear. Sensory cutaneous branches of the anterior cutaneous nerve may be sacrificed. The descendens cervicalis and the branches of the hypoglossal which innervate the strap muscles should be preserved. The omohyoid inferiorly may be sacrificed, if necessary, and the thyroid is then retracted medially and the carotid sheath laterally. For better exposure the inferior thyroid artery and the middle and inferior thyroid vein may be divided. Care is taken during this maneuver to avoid injury to the recurrent nerve. The cricopharyngeus muscle is exposed posteriorly by rolling the esophagus and the inferior pharynx laterally and anteriorly. The muscle is then divided in the midline down to the mucosa carrying the incision cephalad aprozimately 2 cm and caudad approximately 3cm on the esophagus. A plexus of vessels, usually veins, is observed posteriorly in the midline on the cricopharyngeus muscle which must be controlled. The mucosa should bulge out after this maneuver and the surgeon should assure himself at this time that the mucosa has not been violated. The wound is then closed without drainage if excellent hemostasis has been accomplished.

Liquids are permitted on the first postoperative day and increased to a full diet by discharge on the third or fourth day postoperatively.

Discussion

The diagnosis of cricopharyngeal dysfunction causing upper esophageal dysphagia is based mainly on the clinical history and cine studies. We have not found pressure studies of the cricopharyngeus muscle to be helpful. In patients #1,2,4, and 5, pressure studies were normal preoperatively; however, cine studies showed both dilatation and retention in the hypopharynx. Ellis[10] has shown, with manometric studies, premature closure of the cricopharyngeus before the bolus of food in the pharynx is completely emptied into the esophagus in patients with Zenker's diverticulum. However, Kodicek and Creamer[17] have not been able to demonstrate any abnormalities in patients with chronic esophageal diverticula. Resting pressures have been shown to be elevated in the cricopharyngeus in some patients with a pharyngeal diverticulum[14] but Ellis was not able to confirm this.[10]

Ellis[10] has attempted to classify the dysfunction of the cricopharyngeus muscle into four groups: central nervous system disease, diseases affecting muscular activity, post surgical dysphagia, and idiopathic discoordination. The last category which encompasses Zenker's diverticulum or pulsion diverticulum of the upper esophagus may really result from factors in the first two groups, *i.e.* motor neuron or muscular problems.

Mills[21] reported 17 cases of motor neuron disease treated with cricipharyngeal sphincterotomy with 16 patients showing improvement and one immediate postoperative death. He recommends the use of a Zeiss operating microscope to perform the surgery, however, we have not found this necessary. Five of our six cases necessarily fall into the CNS or motor neuron group. Patient #6, with CNS disease, required a permanent tracheostomy for chronic obstructive pulmonary disease. Following the procedure, aspiration was obvious with egress of fluid from the tracheostomy stoma. Cine studies showed holdup at the cricopharyngeus muscle area and aspiration of fluid into the tracheobronchial tree. It is well known that tracheostomy interfers with the swallowing mechanism and this, combined with the patient's CNS disease, appeared to be enough to allow marked dysfunction of the swallowing mechanism. Cricopharyngeus myotomy resulted in improved swallowing without obvious aspiration. Patients with bulbar disease, basilar artery thrombosis, and peripheral neuropathy may be candidates for cricopharyngeal myotomy. Also, severe neuropathy may occur with patients who have carcinoma, and dysphagia may be the major complaint. Neuropathy and a myasthenic-like syndrome is a well known complication of lung cancer. Studies of patients with CNS disease show failure of relaxation of the cricopharyngeus muscle. Dysphagia may be the presenting complaint of patients with muscular dystrophy or myasthenia gravis. Toxic hyperthyroidism may also cause a pharyngeal-cricopharyngeal dysfunction but should respond to the treatment of the primary disease. Inability to develop effective peristalsis in the pharynx appears to be the major dysfunction in patients with myopathies and dysphagia. Esophageal hiatus hernia must be ruled out in patients presenting with dysphagia and apparent spasm of the cricopharyngeus muscle. Belsey[3] reported 3.5% of 829 cases of hiatus hernia had spasm of the cricopharyngeus region and in 10 patients it was the chief complaint. Treatment of the hiatus hernia and reflux resolved the upper esophageal spasm.

Recently, routine cricopharyngeal myotomy has been advised with certain radical, oral, or pharyngeal resections.[5,20,22,23] Cases which should be considered for cricopharyngeal myotomy are vagal nerve injuries, radical glossectomy, radical oral pharyngeal resections, supraglottic laryngectomies and patients who already have dysphagia or a Zenker's diverticulum and are to undergo hypopharyngeal or major tongue resections. Patients with dysfunction of the swallowing mechanism requiring permanent tracheostomy may also be candidates. Mladick et al[20] reported 21 patients in which cricopharyngeal myotomy was performed when radical oral pharyngeal surgery was carried out. Their operative technique is different than that described above. The hypopharynx being open already, the mucosa over the cricopharyngeus is slit posteriorly and the muscle fibers then cut proximally and distally. The mucosa is then closed.

Many papers in the past decade have subscribed to the supposition that the muscles of the pharynx and cricopharyngeus are the precipitating factor in the development of Zenker's pulsion diverticulum. Belsey[3] has presented 32 cases of pulsion diverticula treated with myotomy and usually diverticulopexy with excellent results. And Ellis[10] has also subscribed to the treatment of pulsion diverticulum with myotomy. Case #3 is of interest in that the repeat cine studies showed that the diverticulum had recurred. Cricopharyngeus myotomy alone relieved the patient's symptoms and the patient now two years postoperatively has no difficulty with swallowing. This patient had moderate CNS disease on the basis of his arteriosclerotic vascular disease and it is felt that this was the probable etiology of his swallowing dysfunction.

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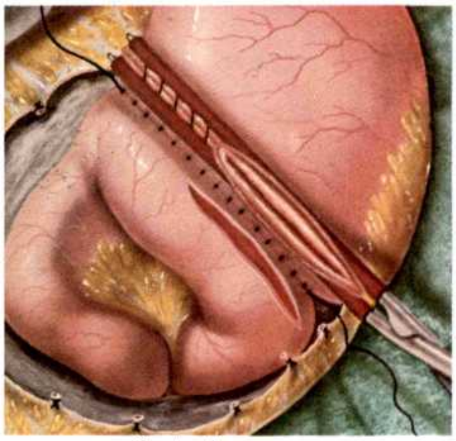
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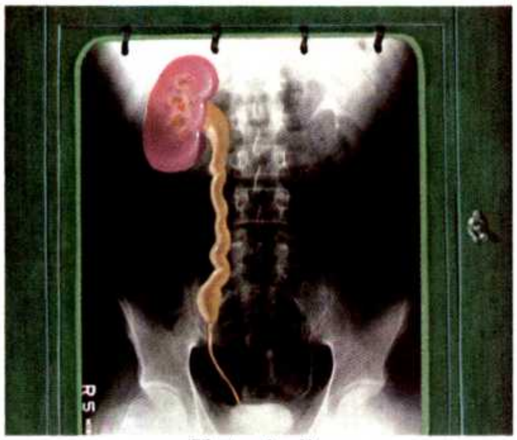

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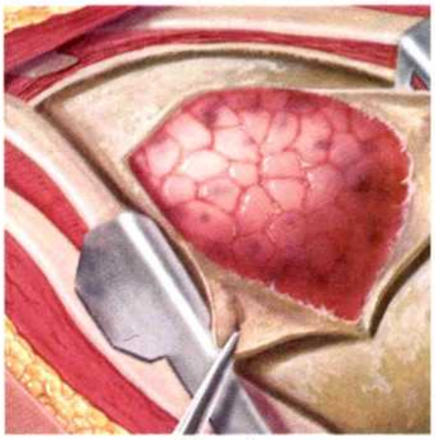
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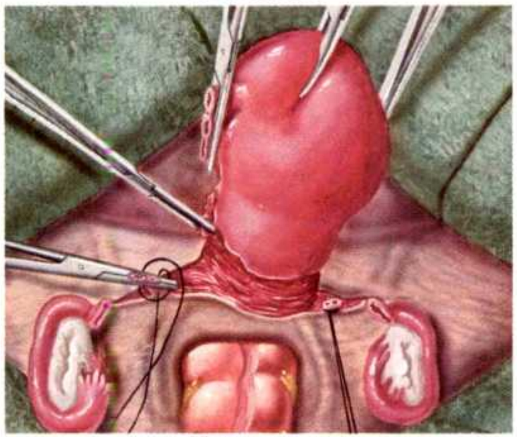
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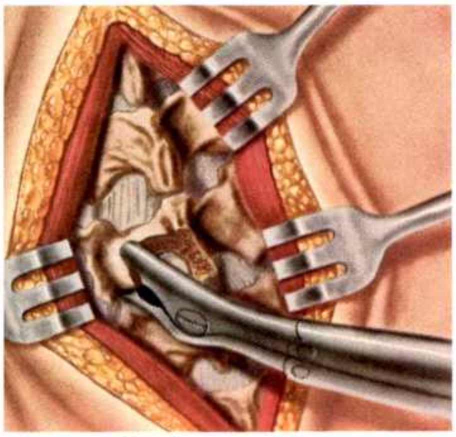
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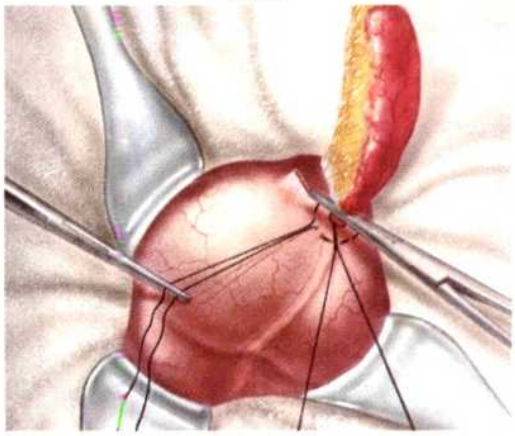
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Since clinical experience in children under 12 years of age is limited, the use of Talwin (brand of pentazocine, as lactate) in this age group is not recommended. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards. See full instructions and warnings on last page.

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Warnings: *Drug Dependence. Special care should be exercised in prescribing pentazocine for emotionally unstable patients and for those with a history of drug misuse. Such patients should be closely supervised when long-term therapy is contemplated. There have been instances of psychological and physical dependence on Talwin in patients with such a history and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in symptoms such as abdominal cramps, elevated temperature, rhinorrhea, restlessness, anxiety, and lacrimation. Even when these occurred, discontinuance has been accomplished with minimal difficulty. In the rare patient in whom more than minor difficulty has been encountered, reinstitution of parenteral Talwin with gradual withdrawal has ameliorated the patient's symptoms. Substituting methadone or other narcotics for Talwin in the treatment of the Talwin abstinence syndrome should be avoided.*

In prescribing parenteral Talwin for chronic use, particularly if the drug is to be self-administered, the physician should take precautions to avoid increases in dose and frequency of injection by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

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Head Injury and Increased Intracranial Pressure. The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

Usage in Pregnancy. Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

Acute CNS Manifestations. Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstituted it should be done with caution since the acute CNS manifestations may recur.

Usage in Children. Because clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

Ambulatory Patients. Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

Precautions: *Certain Respiratory Conditions.* The possibility that Talwin may cause respiratory depression should be considered in treatment of patients with bronchial asthma. Talwin should be administered only with caution and in low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease appears to predispose to greater side effects (e.g., marked apprehension, anxiety, dizziness, sleepiness) from the usual clinical dose, and may be the result of decreased metabolism of the drug by the liver.

Myocardial Infarction. As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

Biliary Surgery. Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

Patients Receiving Narcotics. Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced withdrawal symptoms after receiving Talwin.

CNS Effect. Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

Adverse Reactions: The most commonly occurring reactions are: nausea, dizziness or lightheadedness, vomiting, euphoria.

Infrequently occurring reactions are—*respiratory:* respiratory depression, dyspnea, transient apnea in a small number of newborn infants whose mothers received Talwin during labor; *cardiovascular:* circulatory depression, shock, hypertension; *CNS effects:* sedation, alteration of mood (nervousness, apprehension, depression, floating feeling), dreams; *gastrointestinal:* constipation, dry mouth; *dermatologic including local:* diaphoresis, sting on injection, flushed skin including plethora, dermatitis including pruritus; *other:* urinary retention, headache, paresthesia, alterations in rate or strength of uterine contractions during labor.

Rarely reported reactions include—*neuromuscular and psychiatric:* muscle tremor, insomnia, disorientation, hallucinations; *gastrointestinal:* taste alteration, diarrhea and cramps; *ophthalmic:* blurred vision, nystagmus, diplopia, miosis; *hematologic:* depression of white blood cells (especially granulocytes), usually reversible and usually associated with diseases or other drugs which are known to cause such changes, moderate transient eosinophilia; *dermatologic:* soft tissue induration, nodules, cutaneous depression, ulceration (sloughing) at the injection site, toxic epidermal necrolysis; *other:* tachycardia, weakness or faintness, chills, allergic reactions including edema of the face.

See *Acute CNS Manifestations* and *Drug Dependence* under **WARNINGS.**

Dosage and Administration: *Adults, Excluding Patients in Labor.* The recommended single parenteral dose is 30 mg. by intramuscular, subcutaneous, or intravenous route. This may be repeated every 3 to 4 hours. Doses in excess of 30 mg. intravenously or 60 mg. intramuscularly or subcutaneously are not recommended. Total daily dosage should not exceed 360 mg. As with most parenteral drugs, when frequent daily injections are needed over a prolonged period, intramuscular administration is preferable to subcutaneous. In addition, constant rotation of injection sites (e.g., the upper outer quadrants of the buttocks, mid-lateral aspects of the thighs, and the deltoid areas) is recommended.

Patients in Labor. A single, intramuscular 30 mg. dose has been most commonly administered. An intravenous 20 mg. dose has given adequate pain relief to some patients in labor when contractions become regular, and this dose may be given two or three times at two- to three-hour intervals, as needed.

Children Under 12 Years of Age. Since clinical experience in children under twelve years of age is limited, the use of Talwin in this age group is not recommended.

CAUTION. Talwin should not be mixed in the same syringe with soluble barbiturates because precipitation will occur.

Overdosage: *Manifestations.* Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

Treatment. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

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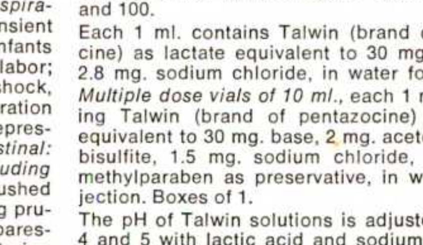

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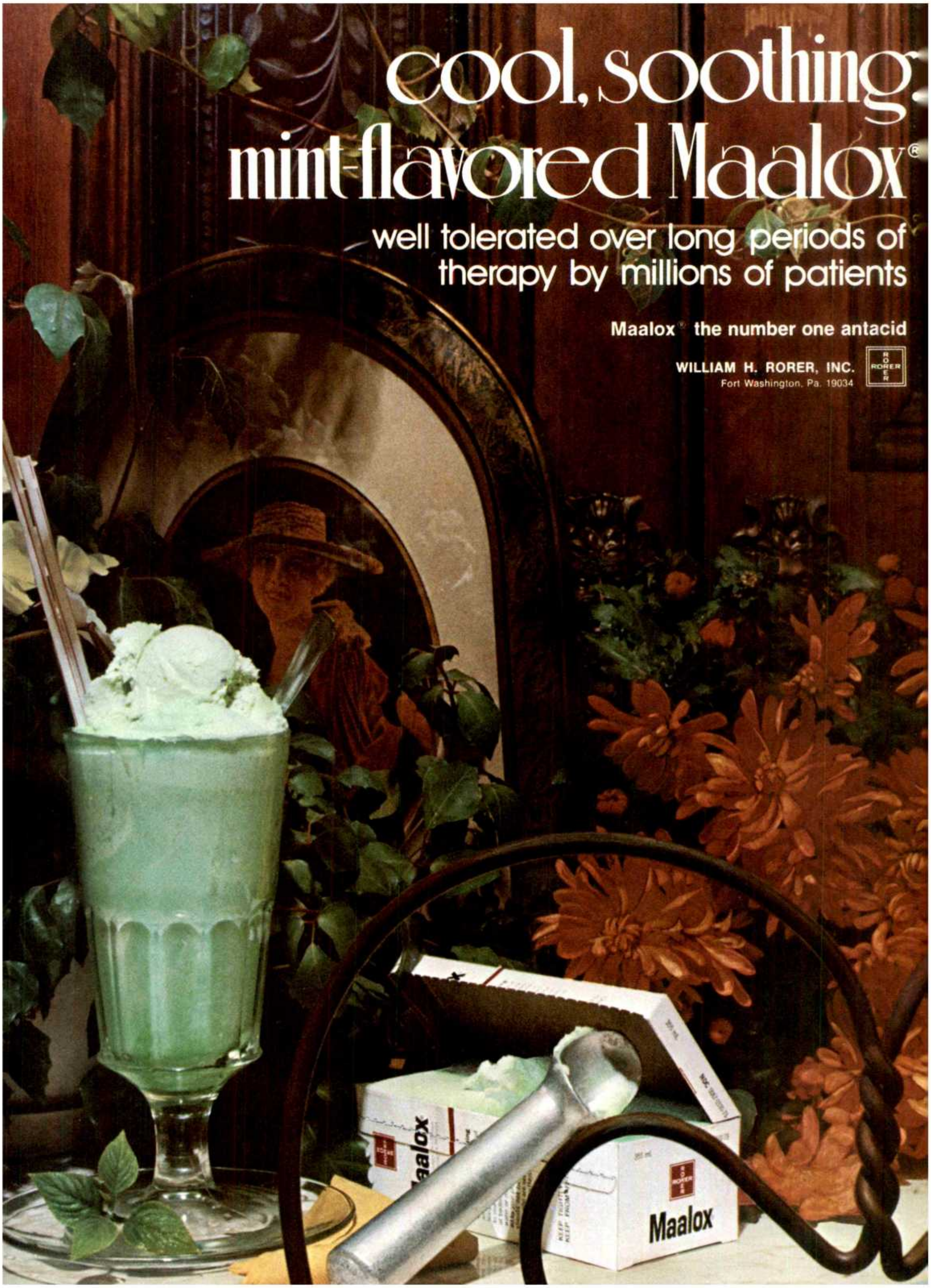
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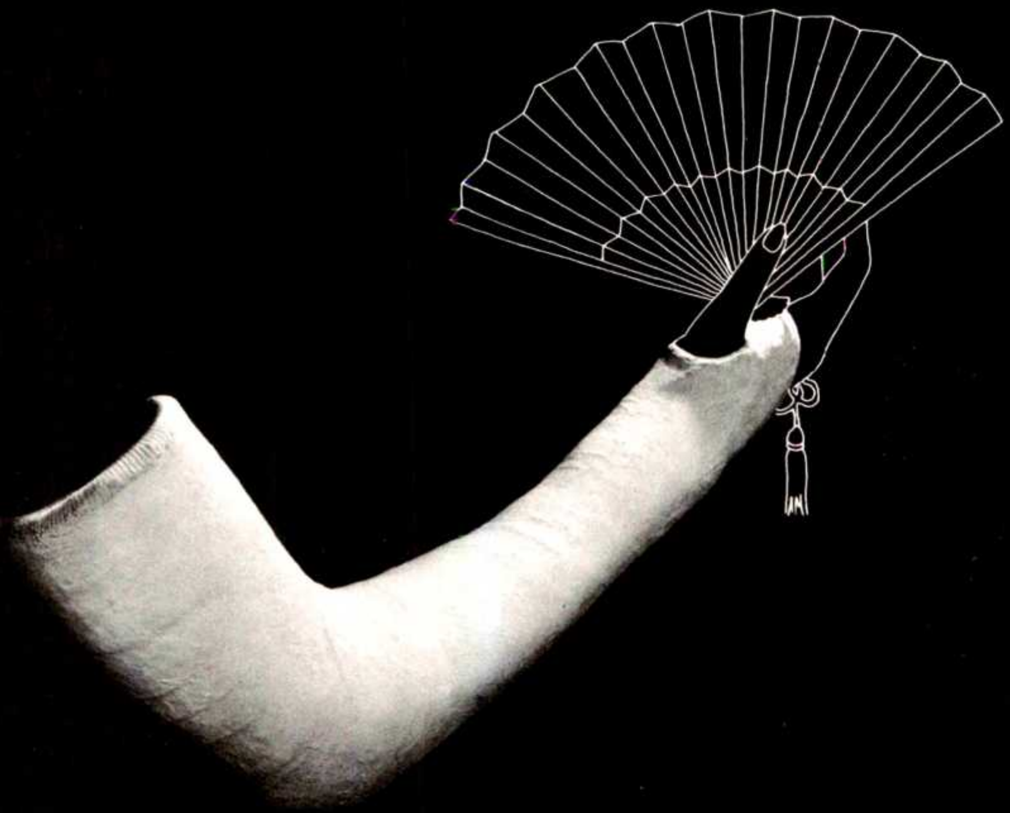

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Spinal Ischemia Following Abdominal Aortic Surgery

LAWRENCE R. J. FERGUSON, M.D., JOHN J. BERGAN, M.D.,
JULIUS CONN, JR., M.D., JAMES S. T. YAO, M.D., PH.D.

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Serious spinal cord ischemia may follow infrarenal abdominal aortic surgery. Five cases are summarized and added to the 23 previously published cases in order to identify this syndrome, emphasize its importance, and draw attention to the possibility of spontaneous recovery which may occur. The multifactorial complex which comprises each patient's clinical picture clouds a precise and specific cause for paraplegia in these cases. However, neither hypotension, steal phenomena nor emboli are necessary for completion of the syndrome. The relevant spinal cord arterial anatomy indicates that the common anomalies which occur favor development of spinal cord ischemia in the arteriosclerotic population which requires aortic surgery. No means of prevention is possible at this time.

PROFOUND lower extremity neurologic deficit with or without bowel and bladder paralysis is a rare complication of abdominal aortic surgery. Despite the infrequency of this condition, its occurrence remains devastating.

Sufficient experience has been recorded to allow definition of distinct clinical syndromes. These have occurred after abdominal aortic surgery for intact and ruptured aneurysms and after surgery for occlusive disease (Tables 1 and 2).

The spinal syndromes may be temporary or permanent, may include sensory and motor deficits with bladder and bowel involvement, and may be due to ischemia induced by arterial clamping or bypass, or may be caused by emboli consequent to aortic manipulation.

The object of this paper is to define these syndromes, illustrate them with cases which will serve as examples, and correlate them with the few cases described in the literature.

Case Report: Syndrome of Lumbar Spinal Cord Ischemia with Sensorimotor Return

Case 1. This 66-year-old white male was entirely well until an asymptomatic abdominal aortic aneurysm was found on routine physical examination. He was admitted to the Wesley Pavilion of the Northwestern Memorial Hospital for resection of this aneurysm. Preoperative evaluation exclusive of the aneurysm was entirely normal, including total serum lipid determination, cholesterol, blood urea nitrogen, fasting blood glucose and serum triglycerides.

An 8 cm abdominal aortic aneurysm was resected and a 22 mm bifurcation graft anastomosed end-to-end to the abdominal aorta 2.5 cm below the renal arteries and end-to-end to the iliac arteries above their bifurcations. Total abdominal aortic clamping time was one hour. After the aneurysm was opened, a large midsacral artery was identified which was oversewn within the aneurysm and was not reconnected to the arterial stream. At no time did hypotension occur during the procedure.

In the postoperative period the patient complained of weakness of both lower extremities. Neurologic examination revealed weakness of hip flexion and of leg extension on the left, similar but not as profound weakness of the right hip flexion and calf extension. Deep tendon reflexes were increased at the knee and ankle level bilaterally.

Rapid resolution of the process occurred during the next five days. As this occurred, a modified Brown-Sequard pattern was seen. There were decreased deep tendon reflexes on the left and decreased position sense with a contralateral decrease in pain sensation with weakness.

Total neurologic recovery occurred in the fourteen day period following graft placement. The patient remains well postoperatively.

At no time was fecal incontinence noted, nor was urinary retention a significant problem in this patient. No sacral sensory impairment was noted.

Comment

This patient illustrates a reversible lumbar spinal cord ischemia occurring after abdominal aortic aneurysm surgery. The lack of vesicorectal disturbance suggests sparing of conus medullaris and sacral fibers from the ischemic process (Table 1). Similarly, the increased knee and ankle reflexes suggest upper motor neuron involvement

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Submitted for publication August 26, 1974.

TABLE 1. *Determination of Level of Spinal Ischemia after Aortic Surgery*

Symptom or Sign	Level of Innervation
Cremasteric Reflex*	L-2, L-3
Knee Jerk	L-3, L-4
Quadriceps Muscle	L-4
Ankle Jerk	L-5, S-1
Plantar Extension	L-5
Plantar Flexion	S-1
Bladder Control	S-2, S-3, S-4
Bowel Control	S-2, S-3, S-4
Anal Reflex	S-2, S-3, S-4

* Cremasteric reflex is first to be lost in paraplegia and first to return in recovering cases.

rather than the monosynaptic conus medullaris reflexes which, if called into play, would be demonstrated as hyporeflexia.

This case is similar in the recovery pattern to several in the literature, though the sacral sparing appears to be unique. The case of Skillman,[19] a 65-year-old male with a ruptured aortic aneurysm who had 90 minutes of hypotension, had paraplegia from the level of L-2 with a flaccid anal sphincter and urinary incontinence. During the postoperative period, there was partial motor and sensory return.

The patient of Zuber et al.[21] is also pertinent. This was a 58-year-old male with a ruptured abdominal aortic aneurysm who had hypotension during his aortic resection. Postoperatively, there was paresis of the legs and thighs with diminished proprioception and vibratory sense, and urinary incontinence. There was total neurological recovery at eight weeks.

The case of Hara and Lipin also falls into this category.[9] This was a 64-year-old male with an abdominal aortic aneurysm who also had a period of hypotension during surgery. Postoperatively, there was urinary retention, a lax anal sphincter, fecal incontinence, but no motor or sensory loss. In this instance, there was also complete recovery. This patient seems to have had sparing of lumbar cord segments with reversible ischemic involvement of sacral fibers.

Several other cases described in the literature are indeterminant but may or may not fall within this category. These are patients who died within the first three week period after surgery and who manifested some degree of sensory or motor clearing of neurologic deficit. These include the case of Mehrez,[14] a 76-year-old male also reported by Hogan and Romanul,[10] as well as the case of Sher and Healy,[18] and the 60-year-old male patient of Bates.[3] Also included are the case of Golden et al.,[7] a 62-year-old male with a ruptured abdominal aortic aneurysm; the case of Pasternak and Ellis,[15] a 60-year-old male with an abdominal aortic aneurysm without hypotension who had paraplegia and then marked motor and sensory return; and the second case of Skillman,[9] a 73-year-old man with a ruptured abdominal aneurysm, 30 minutes of hypotension and a paraplegia to L-2 which was clearing up to death at six weeks.

Finally, the case mentioned briefly in a letter to the editor by Gump,[8] of a patient with a ruptured abdominal aortic aneurysm who had complete motor and sensory loss of both extremities and who sustained full recovery in 12 months, may also fall into the category of reversible spinal cord and conus medullaris ischemia following abdominal aortic surgery.

These cases are similar in that most recovery was in the sensory portion and beginning recovery was identified early in the postoperative period. Recovery was otherwise irregular and, in motor return, auxiliary muscles played a prominent role.

Case Reports: Syndrome of Permanent Lumbar and Sacral Paraplegia

Case 2. A 68-year-old diabetic male entered the Wesley Pavilion, Northwestern Memorial Hospital because of rest pain and gangrene in his left second toe. He was a maturity onset diabetic who had taken 55 U of NPH insulin daily for 12 years. He was also receiving digoxin and a diuretic following an episode of congestive heart failure three years prior to the present admission.

Physical examination showed him to be normotensive, blood pressure 140/90. No peripheral pulses were present in the lower extremities. Gangrene was present in the left second toe and there were marked ischemic trophic changes bilaterally. The electrocardiogram showed old ischemic changes but no recent abnormalities. The arteriogram revealed bilateral common iliac artery occlusions.

Three days following angiography, a bilateral aorto-femoral bypass graft was done using a Dacron prosthesis. A left lumbar sympathectomy was also performed. A large, patent midline lumbar artery was noted arising from the aorta at the level of the fourth lumbar vertebra. This was preserved but was temporarily occluded for 40 minutes during graft placement. During surgery and in the immediate postoperative period, blood pressure was normal. There was no period of hypotension. Urine output was adequate at all times.

In the recovery room and during the first postoperative day, the patient complained of complete loss of sensation below the umbilicus and total leg and thigh paralysis. The extremities showed a flaccid paraplegia, complete sensory level at T-12 - L-1, flaccid anal sphincter, and areflexia in the lower extremities. Postoperative steriods were given to reduce spinal cord edema and subsequently a lumbar myelogram was done, which was negative.

The patient had virtually no neurologic recovery except that he had some control of the sartorius muscles bilaterally, thus demonstrating a degree of L-1 return. He remained paraplegic three years later, with incontinence and sensory status essentially as before. He died at home, unattended, and no autopsy was done.

Case 3. This 56-year-old woman was admitted to the Wesley Pavilion of the Northwestern Memorial Hospital for treatment of severe ischemia of the lower extremities. She was known to have had rheumatic heart disease, arteriosclerotic heart disease, episodic congestive heart failure, transient cerebral insufficiency, and angina pectoris. She had no known recurrence of carcinoma after a radical mastectomy done two years previously.

Physical examination showed blood pressure 120/70, grade I retinopathy, irregular cardiac rhythm, no circulatory congestion. Laboratory studies showed hypercholesterolemia; ECG, atrial fibrillation and T-wave inversion in Lead 2. Retrograde femoral aorto-arteriography showed bilateral aorto-iliac arterial occlusions with extensive ilio-lumbar arterial collateral vessels.

TABE 2. *Summary of all Known Cases of Paraplegia Following Abdominal Aortic Surgery*

Author	Age/Sex	Neurological Deficit	Late Result
Abdominal Aortic Aneurysm			
Coupland & Reeve	59/Male	Flaccid paralysis from L-2, sensory from L-3 Developed 24 hours postoperatively	Permanent paraplegia to T-12
Zuber et al.	74/Male	Paraplegia	Died with no neurologic recovery
Hara & Lipin	64/Male	*No motor or sensory loss*, urinary retention Lax anal sphincter, fecal incontinence	Complete recovery
Bates	55/Male	Paraplegia, sensory level—T-11 Developed 48 hours postoperatively	Died at 11 days, no improvement
	60/Male	Paraplegia, sensory level—L-3 Urinary retention developed 24 hours postop.	Died at 3 months, sensory clearing Motor weakness, no bladder return
Golden et al.	58/Female	Paraplegia, L-1	Persistent weakness, urinary incontinence
Reich	71/Male	Flaccid paraplegia, sensory level—T-12 Fecal incontinence	Died at 21 days, no neurologic recovery
Pasternak & Ellis	60/Male	Paraplegia, no level given	Marked motor, sensory return
Case 2	66/Male	Motor weakness in hips and thighs Sensory level—L-1 Hyperreflexia in both lower extremities No fecal incontinence or urinary retention	Full recovery at 14 days
Case 4	76/Male	Paraplegia, sensory level—L-2	Died at 3 weeks, no improvement Renal failure
Ruptured Abdominal Aortic Aneurysm			
Coupland & Reeve	79/Male	Flaccid paraplegia—T-12 Developed 24 hours postoperatively	Died at 48 hours
Skillman	65/Male	Paraplegia—L-2, first noted 48 hours postop. Flaccid anal sphincter, urinary incontinence	Partial motor and sensory return
	73/Male	Sensory level—L-2, motor weakness	Improving neurological status, died at 6 weeks
Gump	Not Stated	"Complete motor and sensory loss in both extremities"	Almost complete recovery at 12 months
Zuber et al.	75/Male	Paraplegia, urinary and fecal incontinence Subdiaphragmatic cross-clamping	Died at 30 days, no neurologic recovery
	65/Male	Paraplegia, dissociative sensory loss Subdiaphragmatic cross-clamping	Permanent deficit
	58/Male	Paresis of legs and thighs, urinary incontinence Diminished proprioception and vibratory sense	Recovery at 8 weeks
Hogan & Romanul	76/Male*	Bilateral paraplegia, sensory level—L-2 Urinary and fecal incontinence	Sensory cleared, no motor return Died at 24 days
Mehrez	76/Male*	Flaccid paraplegia, sensory level—L-2 Urinary and fecal incontinence	Sensory cleared, no motor return Died at 24 days
	69/Male	Flaccid paraplegia, sensory loss to T-9 Fecal incontinence	Died at 36 hours Spinal cord infarction to L-1
Sher & Healy	82/Female	Paraplegia, preserved touch Flaccid anal sphincter	Died at 40 days Some motor and sensory clearing
Golden et al.	62/Male	Paraplegia, sensory level—L-1 Fecal and urinary incontinence	Sensory return, motor weakness No bladder return
Aorto-Iliac Occlusion			
Lake	46/Female	Motor, sensory paraplegia, hypesthesia to T-10	Vibratory and touch sensation returned
Edmondson & Gindin†	51/Male	Flaccid paraplegia, sensory level—L-1	Died at 10 days, no neurologic recovery
Zuber et al.	72/Female	Paraplegia, no level given	Died at 5 days
Case 2	68/Male	Flaccid paraplegia, sensory level—T-12 Flaccid anal sphincter	Some degree of L-1 return, died at 3 years
Case 3	56/Female	Total saddle anesthesia, sensory loss to L-5 Fecal and urinary incontinence	Died at 2.5 years, myocardial infarction Some proprioceptive return
Case 5	58/Male	Paraplegia to L-1, slow onset over 24 hours	Died at 7 days, no neurologic recovery

*Same patient.
†Aortic aneurysm also present.

Surgical correction included bilateral aorto-femoral graft, lumbar sympathectomy, and cholecystectomy. There was no hypotension during surgery or postoperatively. Brief postoperative tachycardia to 125 immediately responded to lidocaine infusion.

Twenty-four hours postoperatively, neurologic examination revealed total saddle anesthesia, total L-5 sensory loss on the left, and patchy L-5 loss on the right. Bladder and bowel incontinence were present and persistent. Over the next 30 months, some proprioceptive sensibility returned to foot and saddle areas but bowel and bladder control were imperfect. The patient died of acute myocardial infarction and associated arrhythmia two and one-half years postoperatively.

Autopsy findings showed findings in the brain consistent with incidental

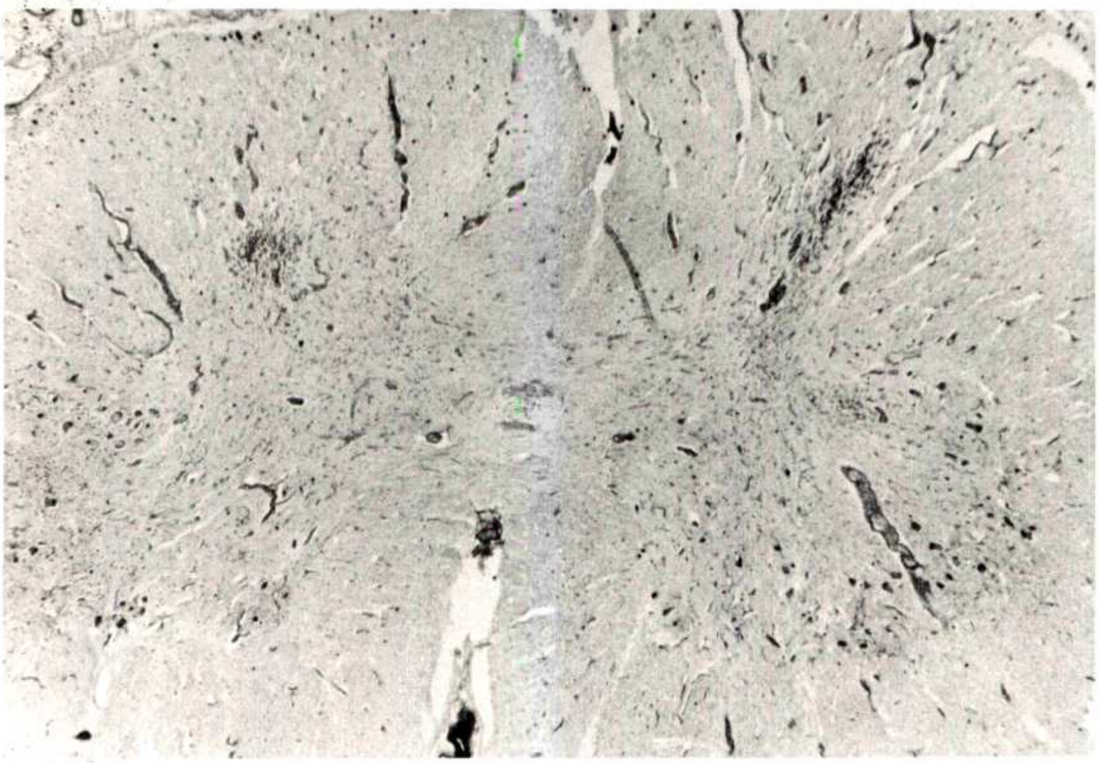

FIG. 1. Photomicrograph of the spinal cord shows perivascular destruction in the dorsal horn areas (×50).

multiple sclerosis. In the lower lumbar and sacral spinal cord, there was focal perivascular destruction in dorsal horn areas (Fig. 1). Many macrophages, gitter cells and siderophages were identifiable (Fig. 2). Widespread necrosis was conspicuously absent.

Thus, in this case, histologic examination of the spinal cord was singularly unrevealing. No clear correlation of neurologic deficit and central nervous system destruction could be made.

Since the gross and microscopic evaluation of the spinal cord was remote from the time of injury, it might be argued that earlier pathologic examination might be more illuminating. That this is not necessarily true is shown by the following case.

Case 4. A 76-year-old white male was admitted to the Passavant Pavilion of the Northwestern Memorial Hospital for elective repair of his abdominal aortic aneurysm. The asymptomatic pulsatile mass had been discovered on routine physical examination. Occular myasthenia gravis had been present and the patient had undergone careful neurologic evaluation. He was hypertensive, diabetic, and had glaucoma. Cataract surgery had been performed three months prior to the present admission.

The blood pressure was 180/85, pulse rate was 78 and irregular. Physical examination revealed the carotid, brachial, radial and femoral pulses to be normal. The right dorsalis pedis pulse was present. Both popliteal pulses and the left dorsalis pedis pulse were absent.

The neurologic findings were consistent with occular myasthenia gravis and an electrocardiogram showed atrial fibrillation with a left hemiblock.

Surgery was performed under spinal anesthetic and an abdominal aortic aneurysm distal to the renal vessels extended to the area of bifurcation. The aneurysm was resected and a Dacron graft was placed distal to the renal arteries and anstomosed end-to-end to the external iliac arteries proximal to the inguinal ligaments. The spinal anesthetic was supplemented with general anesthesia during surgery.

In the postoperative period, the patient had complete sensory loss and lower extremity paralysis which persisted. Initially, the level of paralysis was at L-2 - L-3, but this ascended to L-1 - L-2. The postoperative course was characterized by increasing renal failure, development of patchy gangrene over the lower extremities and toes and, at autopsy, bilateral renal failure was explained by cortical necrosis with multiple embolic occlusions of intrarenal arterioles. Focal subcapsular hemorrhages were seen in the spleen and petechial hemorrhages and gangrene of the toes were also recorded.

Comment

The spinal cord ischemia in this case could not be documented at autopsy. No gross or microscopic changes could be found to explain the neurologic deficit which was so well documented clinically. Various causes could be conjectured: 1) exclusion of spinal cord nutrient arteries in the reconstruction; 2) emboli to spinal arteries; 3) induction of a steal phenomenon; or 4) the spinal anesthesia. In this example, the fact of embolization to kidneys and lower extremities was well documented. Whether or not emboli to ilio-lumbar vessels and ultimately to the anterior spinal artery and its arborization could have ensued is only conjectural. Emboli were clearly proven to have caused spinal cord damage in the case reported by Reich,[17] and were found in the kidneys of one of the patients described by Skillman.[19]

Lake[13] has raised the question of the possible implication of spinal anesthesia with spinal cord damage following abdominal aortic surgery. In his case, a 64-year-old woman with arteriosclerosis obliterans and diabetes mellitus, an infrarenal aorto-iliac bifurcation graft was placed and bilateral sympathectomy performed. The patient had an epidural anesthesia with Lidocaine, 1.5%, and the anesthetic level was maintained at T-6 during the ten hour

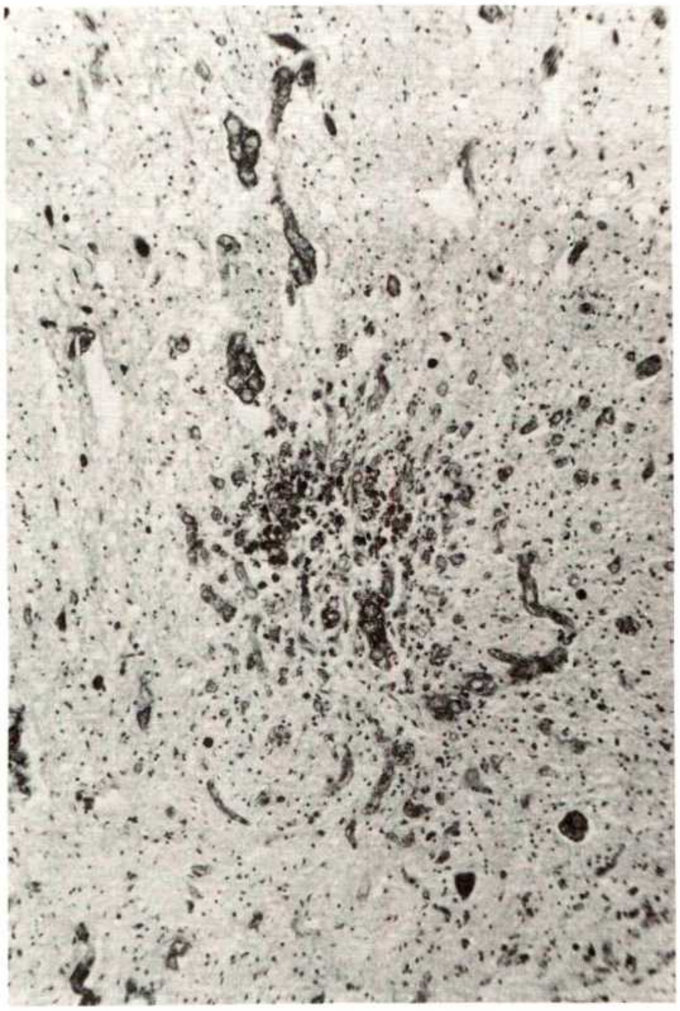

FIG. 2. This photomicrograph shows many macrophages, gitter cells and siderophages in the dorsal horm area (×400).

operation. The patient had persistent sensory loss to T-10. The exact cause of neurologic deficit in his case was not ascertained.

All of these patients illustrate the syndrome of lumbar and sacral ischemia with the areflexia to be expected in conus medullaris involvement. They are much like several in the literature.

The case of Coupland and Reeve,[4] a 59-year-old male with an abdominal aortic aneurysm resected without hypotension also had flaccid paralysis from the L-2 level, sensory loss from L-3 level, and was permanently paraplegic. The case of Zuber et al.,[21] a 65-year-old male with a ruptured abdominal aortic aneurysm who had 60 minutes of hypotension and subdiaphragmatic cross-clamping of the aorta, was paraplegic and had a dissociative sensory loss which was permanent. The case of Golden et al.,[7] a 58-year-old female with an abdominal aortic aneurysm who had a brief episode of hypotension, was also paraplegic to the level of L-1 and had persistent weakness and urinary incontinence.

Multiple other cases may be similar to this but had an indeterminate outcome because of death in the postoperative period. These include cases described by Coupland and Reeve,[4] Edmondson and Gindin,[6] Lake,[13] Zuber et al.,[21] Mehrez,[14] Bates,[3] and Reich.[17]

Discussion

The classical anterior spinal artery syndrome is characterized by paraplegia, rectal and urinary incontinence, loss of pain and temperature sensation, but with sparing of vibration and proprioception sense. This latter sparing is due to arterial supply of the posterior columns of the cord through the posterior spinal arteries arising from the vertebral vessels in the upper portion. Patients sustaining neurologic deficit in the lower extremities after abdominal aortic surgery commonly have loss of posterior column modalities. This is true because the low and mid-thoracic regions of the cord differ from proximal segments in that the posterior spinal artery receives a major contribution from the anterior spinal artery. Therefore, the loss of proprioception sense in these cases (Case 2 above and others) is completely compatible with anterior spinal artery occlusion.

It is curious that paraplegia following abdominal aortic surgery was unreported prior to 1960. Indeed, as late as 1956, Adams and Geertruyden[2] reviewed extensively the problems of neurologic injury following aortic surgery and explained quite well that the lack of spinal cord lesions during infrarenal aortic surgery was probably due to establishment of sufficient collateral blood supply from the thoracically based radicular artery. Clearly, an understanding of spinal cord vascularization is necessary to development of knowledge regarding this condition.

Spinal Artery Arborizations

Normal anterior and posterior spinal arteries are anastomosing channels formed from inter-communicating branches of segmental arteries arising from the aorta. Kadyi[12] has called them tractus arteriosus anterior and posterior.

The intrarterial anastomoses are the anatomical basis of the border areas (Grinzonnen) which are more prone to ischemic change.[22] In reality, the only supplying branches which are constant are the two anterior and posterior branches from the vertebral arteries. From three to ten anterior radicular arteries also supply the cord and originate from the intercostals and lumbar arteries. The main blood supply to the spinal cord in its distal portion is a major artery called the arteria radicularis magna. This is known as the artery of Adamkiewicz. It originates more commonly on the left and was found as high as T-8 by Suh,[20] and as low as L-4 by Kadyi.[12] In its normal location, it is not subject to trauma during abdominal aortic surgery. However, when a more distal origin occurs, interruption of the artery either by the pathologic process itself or by the surgical procedure may lead to infarction of the distal spinal cord and/or cauda equina. This may indeed have been the situation in Case 2 cited above.

It is interesting to note that the posterior spinal arteries, which commonly arise from the vertebral arteries, are actually dependent upon the anterior spinal arteries between the mid-thoracic region and its distal portion. These are united with the anterior spinal arteries by anastomotic loops in the conus medullaris, called the rami cruciantes. Hailal has demonstrated that the artery of Adamkiewicz fills not only the anterior spinal artery but also the radicular branches of the cauda equina and the posterior spinal arteries. This concept, originally postulated by post mortem studies of Adamkiewicz,[1] has now been confirmed angiographically.

Thus, it can be seen that the anterior and posterior spinal vessels are interdependent in distal portions of the spinal cord. Anatomic studies performed on patients with severe atherosclerosis have shown that origins of vessels leading to the anterior spinal artery are commonly encroached upon by atherosclerotic plaques and debris. Jellinger[11] studied 1,037 necropsy cases and showed that spinal cord arteriosclerosis was a significant factor in cases in which there were circulatory disorders of the spinal cord. He found that ostia of vessels supplying the cord were encroached upon by atheromata and calcific plaques. Such impingement upon the arterial supply is aggravated by unequal growth of the spinal column and the cord, which causes a <90° angle in segmented arteries supplying the anterior spinal artery. He pointed out that the origins of vessels supplying the anterior spinal artery have an abrupt right angle takeoff from the aorta, and that partial stenosis or occlusion of the orifice has a profound effect upon lowering blood pressure in the arteria radicularis magna. It was also shown by Hailal that anterior spinal artery tributaries form a hairpin curve from the major feeding vessels; this angle is caused by unequal growth of the spinal cord and the spinal column.

The phenomenon of circulatory autoregulation in the spinal cord is poorly understood but it is generally thought to parallel that of the brain. Therefore, acquired circulatory disturbances such as aortic atherosclerosis, atheroembolization to the radicular artery, or arterial shunting away from the main radicular tributaries could cause profound hemologic deficit in the distal spinal cord, particularly in the diseased state.

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Filtration Characteristics of Three New In-line Blood Transfusion Filters

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Three types of microemboli filters were examined with the scanning electron microscope. The single layer 40 μ pore filter traps aggregates in the pores. These aggregates are extruded and pass on with the blood and can be demonstrated in a Dacron wool filter downstream. The polyurethane foam filter is an in depth multiple pore filter of variable pore size. This filter allows many aggregates to escape through the pores in the beginning of a transfusion and these aggregates were seen in a Dacron wool filter downstream. As aggregates become trapped, the pore sizes decrease, filtration improves, and flow through the filter becomes reduced. The Dacron wool filter absorbs the particulate material to the fibers of wool. This filter has a large capacity and was not observed to leak aggregates even when subjected to high filtration pressures.

THERE IS CONSIDERABLE EVIDENCE that during storage of blood, platelets and leucocytes become adhesive and form aggregates ranging up to about 200 μ in diameter.[16] These aggregates with other debris have been demonstrated by direct observation,[16] screen filtration pressure,[7-9,16] and Coulter counter[14] methods. Even though standard clot filters with 170 μ pores[11] have been shown to remove approximately 4.5 gm of debris per unit of 21-day-old blood, the Coulter counter method has demonstrated up to 100,000 such aggregates/cc of blood under 170 μ in diameter, even after passage of the blood through such a clot filter.[14] It can be presumed that the majority of aggregates under 170 μ in diameter are infused into the patient.

The present study was designed to compare the means by which three currently available filters remove microemboli from the blood.

Materials and Methods

The three types of microemboli filters evaluated were the Bentley Polyfilter (PF-127) Infusion Blood filter (Bentley Laboratories, Inc., Santa Ana, California), the Ultipor Blood Transfusion Filter (Pall Corporation, Glen Cove, New York), and the Swank Dacron Wool Infusion Blood Filter (Pioneer Filters, Beaverton, Oregon). The Bentley Polyfilter (PF-127) consists of a polycarbonate casing containing a polyester screen filter with a pore size of 236 μ and a sponge-like filter element made of polyester urethane several mm thick. The Ultipor filter consists of a polypropylene casing containing a polyester mesh with a pore size in the 40 μ range and has a filtration surface area of 186 cm². The Swank Dacron wool filter consists of a polycarbonate casing containing a mesh filter with a 170 μ pore size below which is 1.0 gm of loosely packed and, finally, 3.0 gm of tightly packed Dacron wool filaments 17 μ in diameter, providing a total filtration surface area of approximately 7,000 cm².

Blood was drawn from donor dogs under standard blood bank conditions, into sterile nonpyrogenic evacuated glass bottles containing acid citrate-dextrose (ACD) anticoagulant in a concentration equivalent to that in human banked blood (67.5 ml ACD solution per 450 ml whole blood). After five days of storage at 4 C, multiple units of dog blood were mixed together to insure homogeneity and divided into five groups for filtration under gravity flow. In Group I, blood was first filtered through a Dacron wool filter and then through an Ultipor filter. In Group II, blood was first filtered through an Ultipor filter and then through a Dacron wool filter. In Group III, blood was first filtered through a Polyfilter and then through a Dacron wool filter. In

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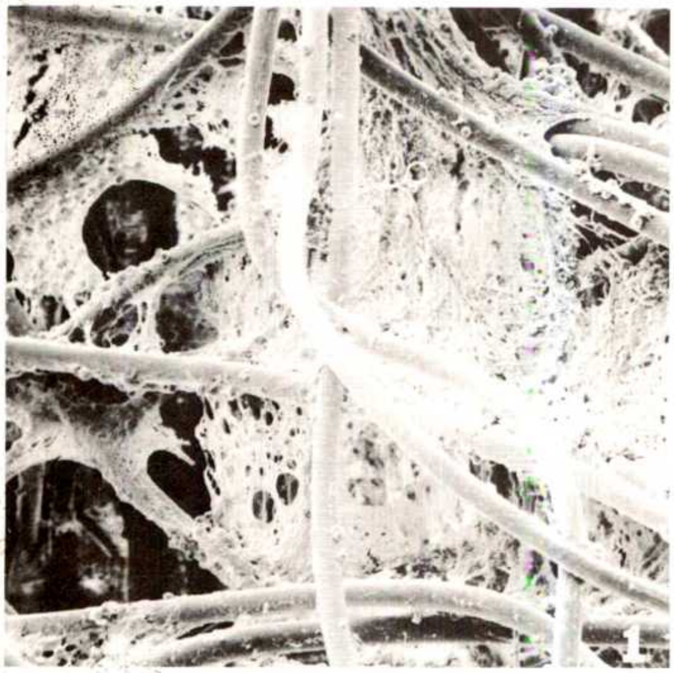

FIG. 1. Scanning electron micrograph demonstrating platelet-leucocyte aggregates and fibrin debris caught in the fibers of a Dacron wool filter after passage of 500 ml of 5-day-old ACD anticoagulated canine blood (Group I). The filter was flushed with 1000 ml of saline to wash out all non-adhering material.

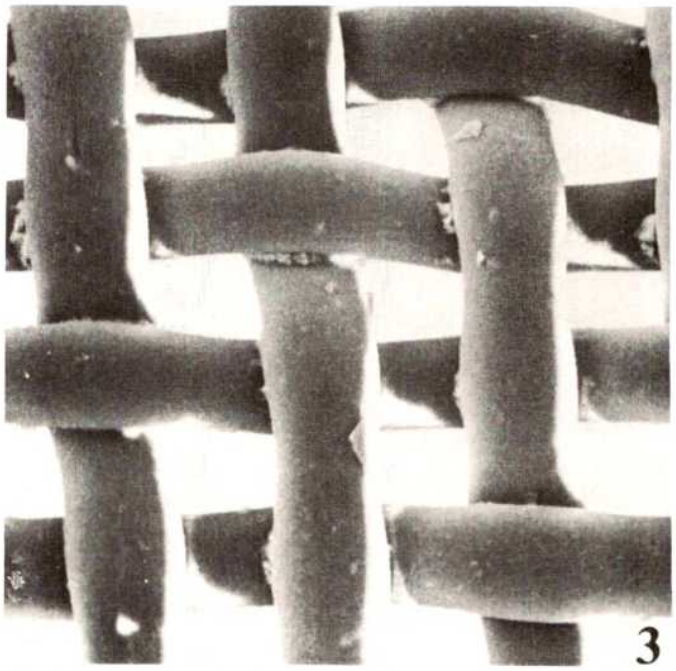

FIG. 3. Scanning electron micrograph of a Barrier filter placed downstream from the Dacron wool filter seen in Fig. 1 (Group I). Following the passage of 500 ml of 5-day-old ACD anticoagulated blood, no detectable platelet-leucocyte aggregates or fibrin debris leaked from the Dacron wool filter and trapped in the Barrier filter.

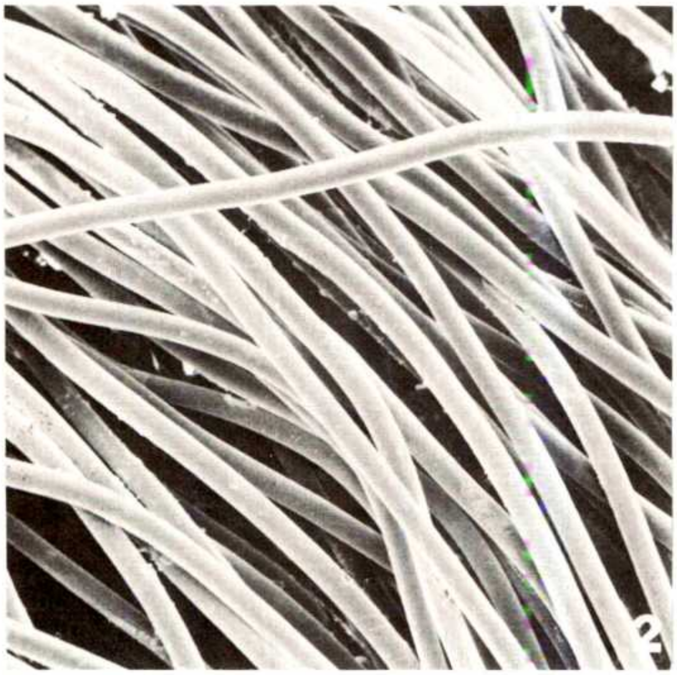

FIG. 2. Scanning electron micrograph of a Dacron wool filter placed downstream from a Dacron wool filter (Group V). Note that few if any platelet-leucocyte aggregates or fibrin debris passed through the first filter to the second filter. Also no platelet-leucocyte aggregates were generated by the Dacron wool in the second filter.

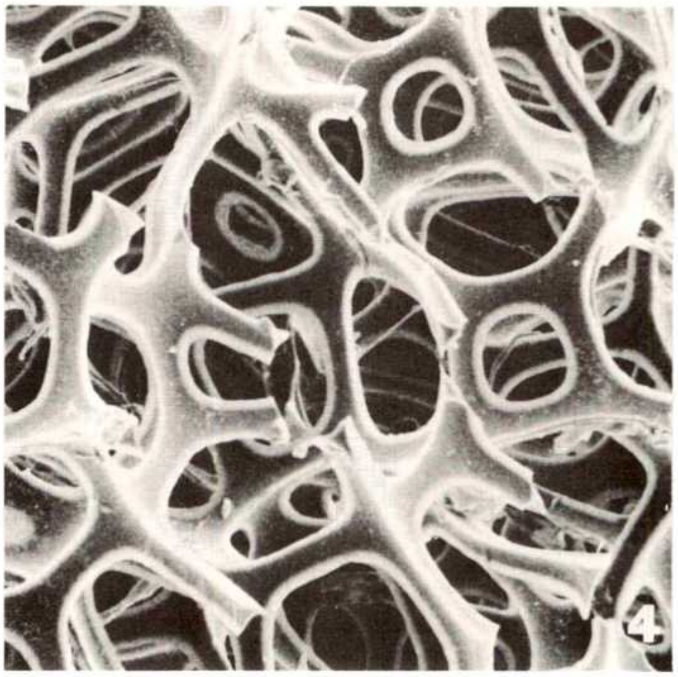

FIG. 4. Scanning electron micrograph of a Bentley polyurethane foam filter placed downstream from a Dacron wool filter (Group IV). Following the passage of 500 ml of 5-day-old ACD anticoagulated blood, no detectable platelet-leucocyte aggregates or fibrin debris were leaked from the Dacron wool filter and trapped in the Bentley polyurethane filter.

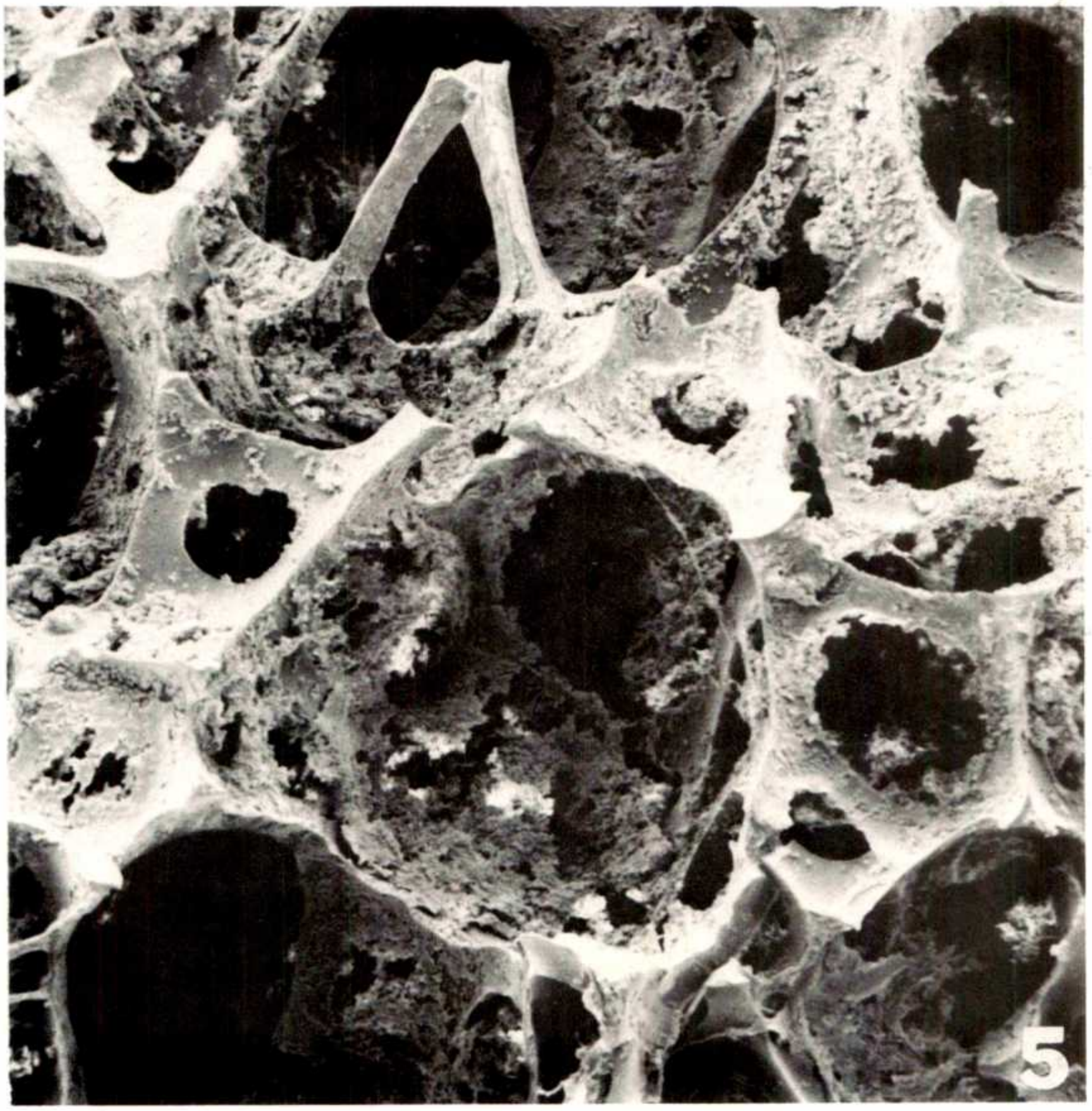

FIG. 5. Scanning electron micrograph of the Bentley polyurethane foam filter after the passage of 500 ml of 5-day-old ACD anticoagulated blood (Group III). The filter was then flushed with 1000 ml of saline to wash out all non-adhering material. Note the aggegate material trapped in the polyurethane foam.

Group IV, blood was first filtered through a Dacron wool filter and then through a Polyfilter. In Group V, blood was filtered through two consecutive Dacron wool filters. Human blood from the blood bank approximately 3 weeks old was experimentally treated in the same ways.

Following filtration, the filters were washed free of non-adhering materials in the direction of blood flow with 1000 cc of physiological saline. Samples of the filters taken from the inlet to the outlet surfaces were fixed for one hour with three percent glutaraldehyde buffered to pH 7.4 with 0.1 M sodium cacodylate and progressively dehydrated in a graded series of ethanol and then in an increasing ratio of Freon to ethanol. The samples were then dried in a Bomar Critical Point Dryer at 40 C under 900 lb/in with a gas escape rate of 50 lb/30 seconds. After making the samples electrically conducting by coating in a vacuum chamber with a layer of evaporated gold-palladium alloy, the samples were examined for aggregate material with a Cambridge stereoscan S_4 scanning electron microscope. For further identification of the particulate debris adhering to Dacron filaments, filter samples were initially fixed as above, postfixed for one hour in one percent osmium tetroxide buffered to pH 7.4 with 0.1 M sodium cacodylate and processed for examination with an RCA EMU 4B electron microscope.

Results

A scanning electron microscopic examination of the filters demonstrated that the Dacron wool filter removed virtually all particulate debris including platelet-leucocyte aggregates from the blood in Groups I, IV, and V (Fig. 1). Little if any aggregate material passed through the first Dacron filter in group V to the second Dacron wool filter downstream from it (Fig. 2). Also, no detectable aggregates or particulate materials were found in the Pall Ultipor 40 $\mu \times 40$ μ filter in Group I

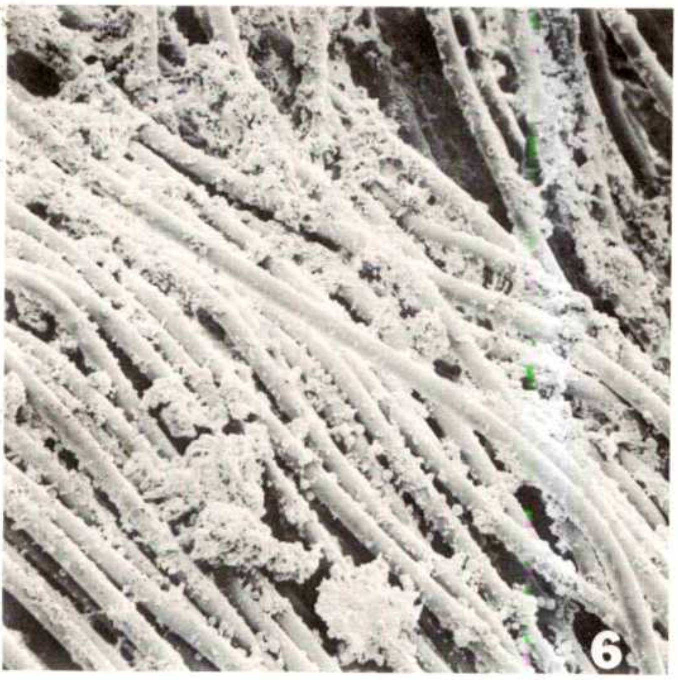

FIG. 6. Scanning electron micrograph of a Dacron wool filter placed downstream from the Bentley polyurethane filter seen in Fig. 5 (Group III). The Bentley filter leaked numerous platelet-leucocyte aggregates in the 10-30 μ diameter range which were trapped in the Dacron wool filter below.

(Fig. 3), or Bentley Polyfilter in Group IV (Fig. 4) downstream from the Dacron filter. The Bentley filter in Group III rapidly became occluded by aggregates (Fig. 5) yet leaked numerous aggregate materials mostly in the 10–20 μ range, and an appreciable number in the 30–40 μ diameter range before the pores became occluded by the aggregates. These were trapped in the Dacron wool filter below (Fig. 6). The Pall Ultipor filter in Group II also rapidly became occluded (Fig. 7) and subsequently leaked many aggregates by the process of extrusion of aggregates through its pores. These were then trapped in the Dacron wool (Fig. 8) downstream. A transmission electron microscopic examination of Dacron wool identified the adhering particulate debris as platelets and leucocytes (Fig. 9).

Discussion

When one considers the very large number of adhesive particles and aggregates which accumulate in blood stored for transfusion (up to 50,000,000/500 cc unit of blood 3 weeks old),[14] it is clear why improved methods of filtration are under development. Animal studies demonstrated that efficient filtration with Dacron and glass wool improved the circulation generally, and in isolated heads maintained normal electrical activity of the brain for prolonged periods,[17] and normalized some metabolic parameters and vascular resistance.[1] In other studies, lung vascular resistance remained normal when aged blood being infused was first filtered through a Dacron wool filter.[10] Otherwise the vascular resistance increased. Further, it has been shown ultrastructurally that obstructive and degenerative lesions occurring in the canine lungs, brain, kidney and liver due to platelet-leucocyte aggregates in transfused blood are prevented by filtering the infused blood through a Dacron wool filter.[4–6]

In human beings the effects of these particles from stored blood have been observed in combat casualties infused with many units of stored blood.[8] The so-called shock lung resulted in which PO_2 values fell sharply and pulmonary vascular resistance increased.[8] Similar occlusive changes in the microvasculature of the lungs occur during use of the extracorporeal circuit in heart surgery,[2] and have been demonstrated by electron microscopy.[3] Filtration of all donor blood infused into the patient and all suction blood from the chest cavity has been shown to practically eliminate the occurrence of post-cardiotomy delirium[12] and remarkably improve the appearance of the fine structure of the lungs. The addition of filtration of the arterial blood has further improved the structural appearance of the lung.[3]

The several types of filters now in use have different characteristics and remove particulate material in different ways. Standard Screen blood filters having 170-220 μ pores remove the largest aggregates and coarse debris

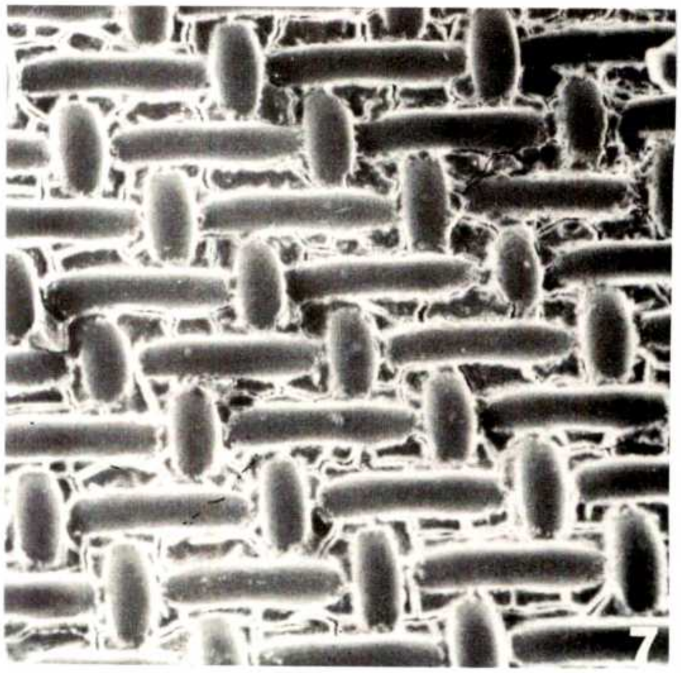

FIG. 7. Scanning electron micrograph of the Barrier filter after the passage of 500 ml of 5-day-old ACD anticoagulated blood (Group II). Note that the 40 × 40 μ pores are obstructed by particulate debris.

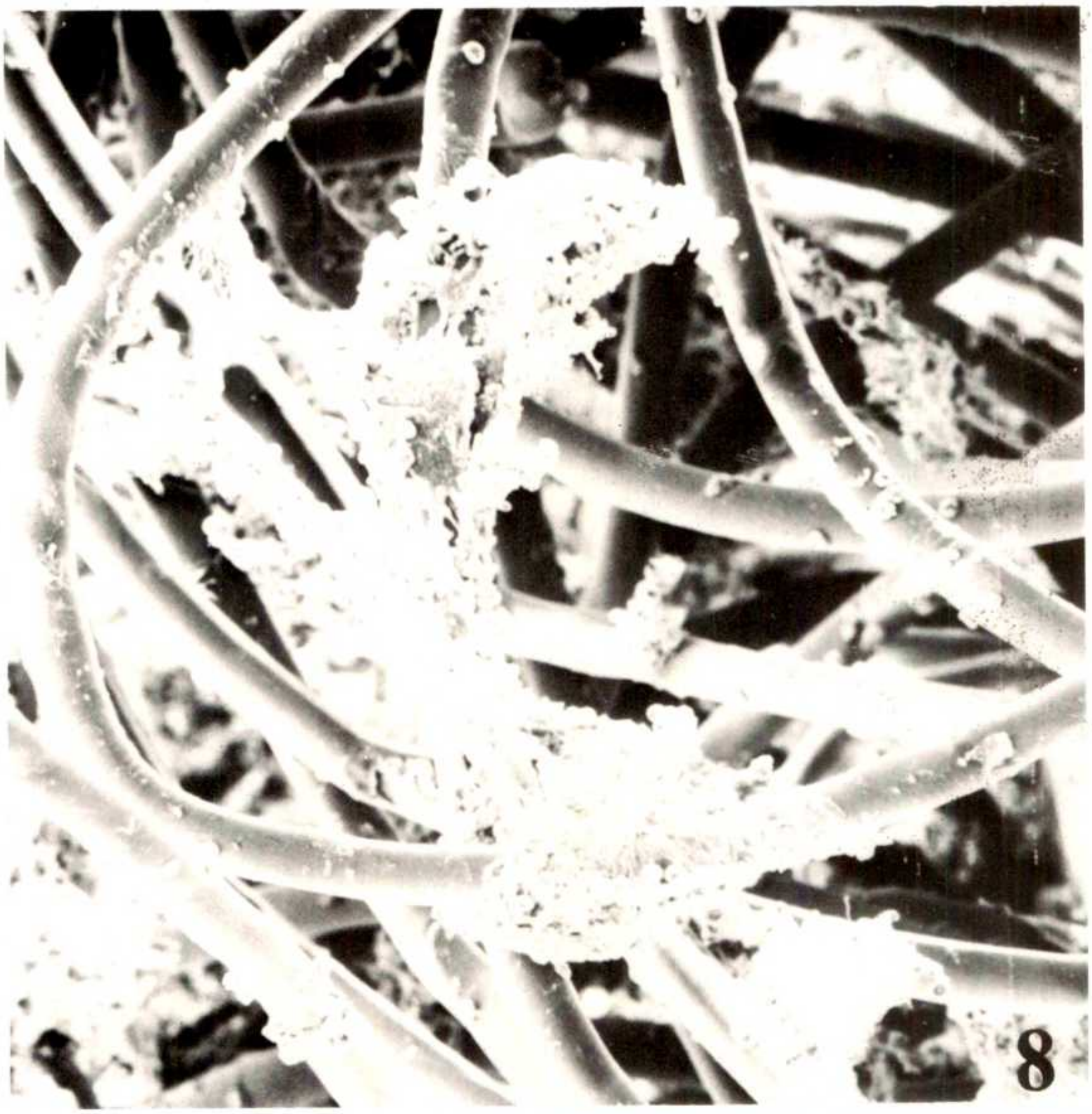

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FIG. 8. Scanning electron micrograph of a Dacron wool filter placed downstream from the Barrier filter seen in Fig. 7 (Group II). The Barrier filter leaked many platelet-leucocyte aggregates and fibrin debris, by the process of extrusion through its pores, which were trapped in the Dacron wool filter below.

from the blood. As the material collects in the filter, its pores narrow, and the efficiency of filtration increases slightly. The screen filtration pressure (SFP) of the blood, which is a measure of the resistance of blood flow through a screen with multiple pores 20 μ, is altered very little by such filtration[16] and size-count studies[14] indicate very little if any removal of particles under the 170 μ size. The introduction of the 40 μ pore size screen filters by Patterson[13] (manufactured by Pall Corp.) was designed to remove smaller aggregates. The studies of Solis and Gibbs[14] indicate, however, that particles 40 μ and smaller pass through this filter without significant alteration of their concentration in the blood. These make up more than 90% of all particles under 170 μ in diameter.[14] Only slight reduction in the SFP by this type of filtration occurs until the filter has become largely occluded. This filter continues to leak aggregates with gravity pressure by the simple process of extruding the particles occluding the pores of the filter.

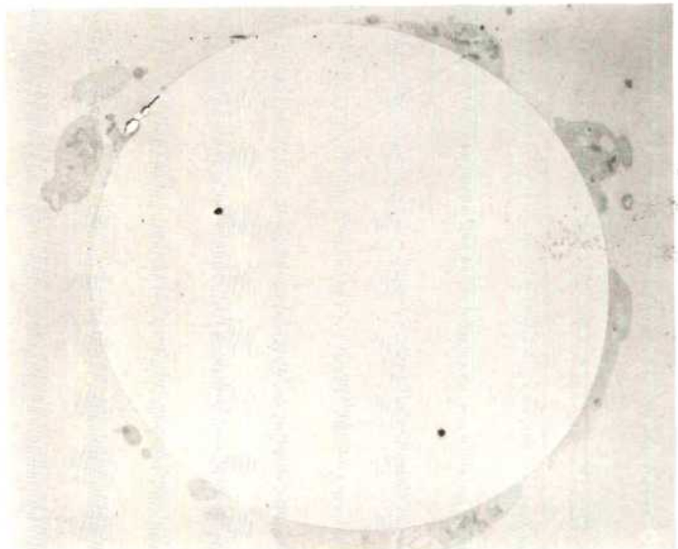

FIG. 9. Transmission electron micrograph of a Dacron wool filter from Group I demonstrating platelet-leucocyte material absorbed to a single Dacron wool filament approximately 17 μ in diameter.

The urethane foam filter introduced by Bentley has so far received very little study. It is an in depth multiple size pore filter. In the present study, it was shown that the current one layer model leaks badly at the beginning of transfusions. As the filtration continues, the pores of this filter become smaller, due to collection of debris in the pores of the foam, and the efficiency of filtration increases. The filter does not become very efficient until it is almost completely occluded and flow has practically stopped. At this time increasing the pressure before the filter increases the SFP some, but not as much as in the former single layer screen type filters.

The Dacron filter relies on two layers of packed wool, the one above loosely packed, the lower more tightly packed. The filter functions by absorption of adhesive materials to the woolen fibers. Pore size cannot be a major factor since the pores average about 95 μ across, which is many times the size of most of the particles removed. The total surface area of the Dacron fibers approximates 7,000 cm^2 in the transfusion filter. It has been calculated that a small particle traversing this filter will contact approximately 100 fibers per cm if pursuing a straight course. This results in a highly efficient filter for all sizes of adhesive particles or other debris down to and less than 10 μ in diameter.[15] SFP and Coulter counter studies have uniformly shown this type of filtration to be highly efficient. Its superiority to the other filters investigated in this paper is shown in that it regularly removed all size aggregates from blood, whereas the single layer screen and foam type of filters regularly leaked aggregates up to 30-50 μ in diameter.

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Metastatic Cystosarcoma Phylloides in an Adolescent Girl:

An Unusually Malignant Tumor

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The first case of metastatic cystosarcoma phylloides in an adolescent is reported. This case also represents the first reported response of this tumor to chemotherapy and irradiation. This tumor showed an unusually rapid rate of cell division probably making it more susceptible to these agents. The importance of an early diagnosis and definitive excision is stressed.

CYSTOSARCOMA PHYLLOIDES is a rare lesion with fewer than 400 cases reported to date in the English literature. Muller,[13] in 1838, gave the first full description of this entity. He emphasized its benign nature. It was not until 1931 that Lee and Pack[7] described the first case of metastasis thus establishing the malignant potential of cystosarcoma phylloides. Since then, approximately 66 other cases with metastasis have been reported.[6] Several excellent reviews of this disease have been published[8,10,11,18–20] with the most recent being that by Kessinger[6] in 1972.

Approximately 34 cases[1,2,5,8,9,11,12,14,16,17,20,22] of cystosarcoma phylloides have been reported in females less than 20 years of age. Of these, all but four have been benign. The four malignant cases[5,9,14,16] were all treated successfully by surgical means with all patients alive when last reported. There have been no reported cases with metastatic disease or death due to this disease in an adolescent. The purposes of this report are to describe the first known case of metastatic cystosarcoma phylloides in an adolescent, as well as, the first reported response to chemotherapy and radiation therapy.

Case Report

R.M., a 14-year-old Romanian female, presented to the Oncological Institute in Bucharest on 11/20/72, with a right breast tumor of four months' duration. Past medical history was noncontributory. Menarche was at age 12 and her periods were regular. Physical exam was unremarkable except for a 10 cm polylobulated, discrete, nontender, freely mobile tumor mass in the right breast. The overlying skin was shiny, tense and reddened but not fixed to the tumor. The left breast and both axilla and supraclavicular areas were negative.

Mammography was interpreted as showing benign fibroadenoma. The needle biopsy was read as benign cystosarcoma phylloides. Chest x-ray, hematologic and chemical profiles were all normal.

On 12/6/72, a frozen section confirmed benign cystosarcoma phylloides, and a simple subcutaneous mastectomy with resection of the external mammary lymph nodes was performed. The tumor was soft, precisely delimited and free of muscle invasion. The final pathology report, however, revealed malignant cystosarcoma phylloides (Fig. 1). All lymph nodes showed reactive changes only.

Three weeks postoperatively a 1.5 cm recurrence was noted in the medial portion of the submammary incision. Within one week it had grown to 4 cm. Needle biopsy confirmed recurrent malignant cystosarcoma phylloides. On 1/12/73, a radical mastectomy was completed with excision of the entire previous incision. At operation the recurrence was found to extend into the pectoralis major muscle. Also, an unsuspected 1 cm nodule of tumor was found in the low posterior axilla during the axillary dissection. This was not a positive lymph node, but was presumably a tumor implant from the initial procedure. The pathology report revealed all axillary nodes to be negative. Because of the unusually aggressive behavior of this tumor, the patient was referred to the National Cancer Institute in Bethesda, Maryland for consultation.

When first seen at the NIH on 2/21/73, there were no signs of disease on physical exam and an extensive metastatic workup. However, on 3/4/73, she developed a 5 mm nodule in the right anterior axilla. Three days later this had expanded to 4 cm and was fixed to the skin. Fine needle aspiration revealed recurrent tumor. The tumor continued to literally explode in growth on the chest wall. She was admitted to the Surgery Branch, NCI, on 3/11/73, with the tumor in the right axilla measuring 8 x 10 cm and extending around the upper chest wall to which it was firmly fixed (Fig 2). Full chest tomograms were negative. On 3/14/73, a right interscapulothoracic amputation and partial resection of ribs three and four were performed. Tumor was found on the axillary vessels high in the axilla and the scapula was invaded.

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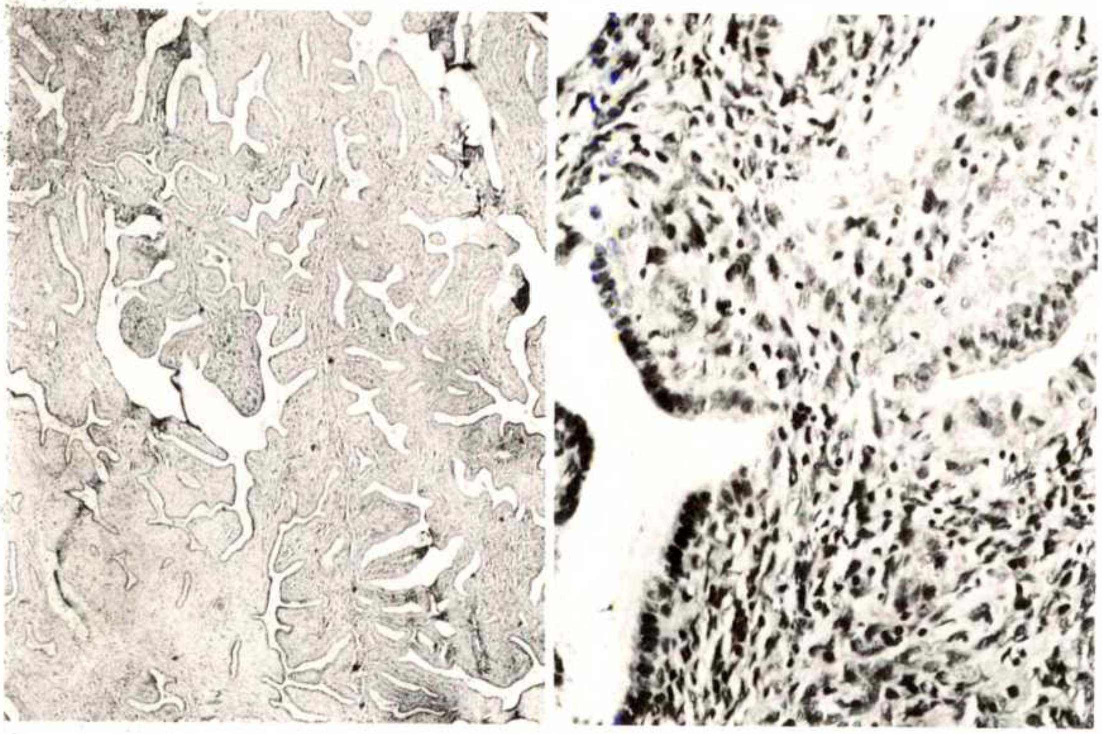

FIG. 1. Photomicrographs of a representative field of the primary breast tumor showing glandular structures lined by normal appearing breast epithelium and malignant appearing sarcoma-like stoma. (Left, x35; right, x350)

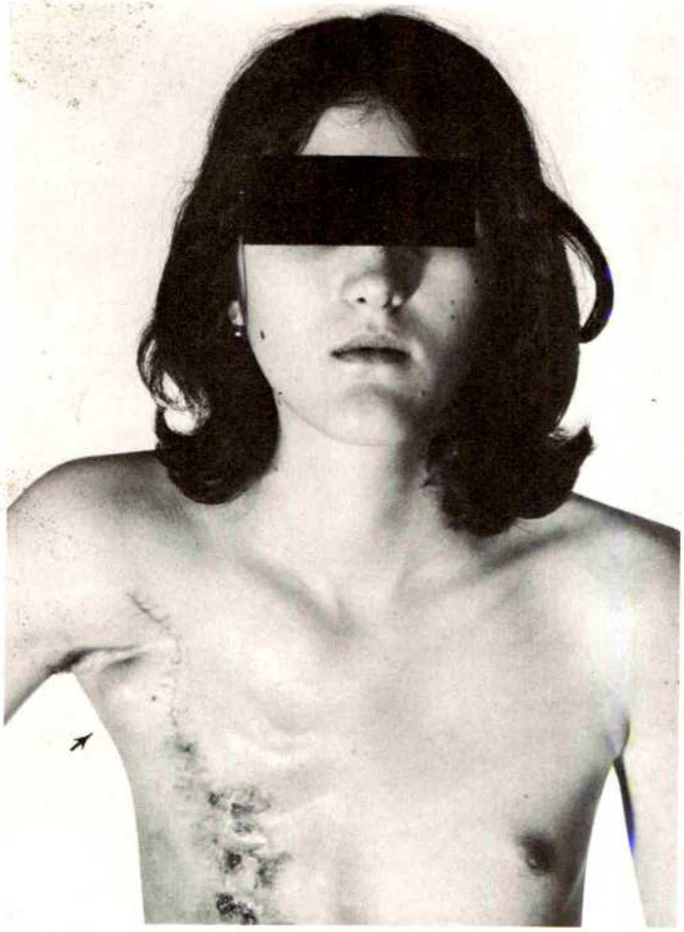

FIG. 2. The rapidly expanding right upper chest wall recurrence can be appreciated in this photograph taken two days before resection.

Lyophilized fascia lata homograft was used to close the chest wall defect. The pathology report revealed the usual histologic pattern of recurrences in this disease with all sections composed of tightly packed sarcoma cells with no glandular structures seen (Fig 3). The tumor had infiltrated widely into the serratus anterior muscle, subcutaneous tissue of the axilla and had attached to, but not penetrated, the periosteum of the ribs. The postoperative recovery was rapid. However, a chest x-ray on the third postoperative day showed a solitary 5 mm nodule in the left mid-lung field. Two weeks later the nodule had doubled in size but repeat tomograms did not reveal other metastases. Exploratory thoracotomy on 4/2/73 revealed only the solitary 1 cm nodule which was removed by wedge resection. The tumor was quite necrotic but was clearly metastatic cystosarcoma phylloides (Fig. 4) with only the stromal part of the tumor represented. The postoperative course was uncomplicated and the patient returned to Romania on 4/17/73, with no sign of disease.

On 5/3/73, the patient's state of health suddenly deteriorated with the development of nausea, anorexia and malaise. Two tumors of 2 cm each were noted subcutaneously in the right upper back, and a 4 cm solitary metastasis was noted in the left lung. Three days later the subcutaneous lesions had doubled in volume and a new 3 cm. tumor was noted in the left supramammary tissues. Intravenous Endoxan (Cyclophosphamide) 200 mg/day was started. During the first week the tumors continued to grow with the tumors on the upper back becoming confluent to form a giant mass of more than 10 cm diameter. After 3 gm (15 days) of Endoxan, the back tumor stopped growing and then decreased to one-half its former size. The left supramammary tumor completely disappeared. The pulmonary lesion also grew progressively smaller until after 5 gm of Endoxan, no signs of tumor existed anywhere. A platelike scar only remained in the lung (Fig. 5). No serious hematologic changes occurred. The patient felt very well and resumed her activities at school.

On 6/10/73 a new 1 cm tumor developed on the right mid-back. It doubled its volume in three days, and small new tumors appeared above it. The patient received cobalt therapy in a field of 8 x 13 cm to a dose of 2505 rads with 7507 rads given to the central 4 x 4 cm field. When the treatment ended on 6/23/73, the largest tumor was di-

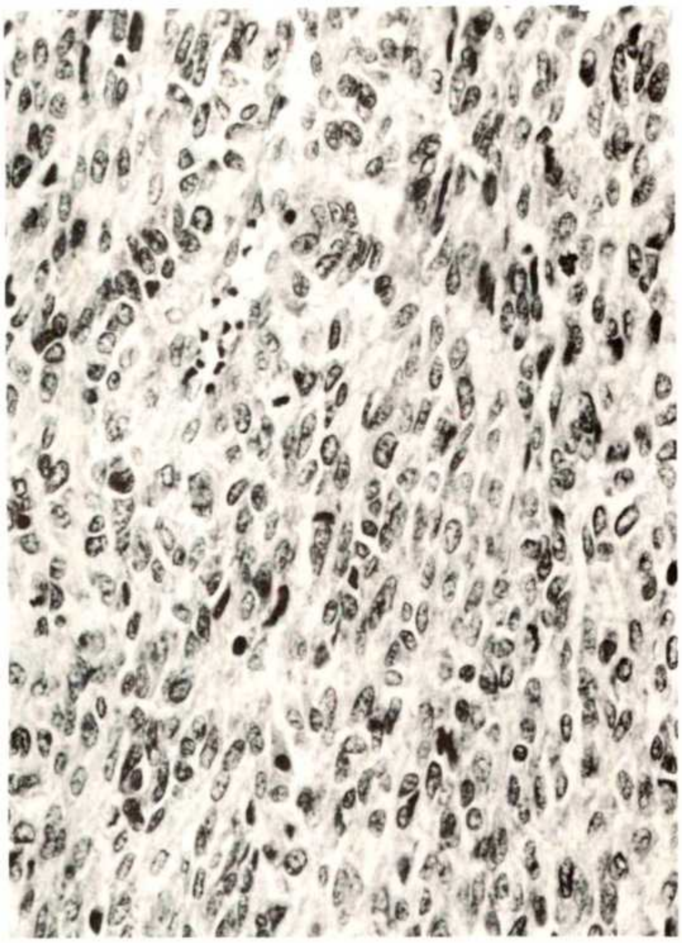

FIG. 3. A photomicrograph of the tumor recurrence on the chest wall showing tightly packed sarcoma cells characterized by large, watery nuclei and irregular, pale staining cytoplasm without definite cell membranes. Mitotic figures were numerous (x350).

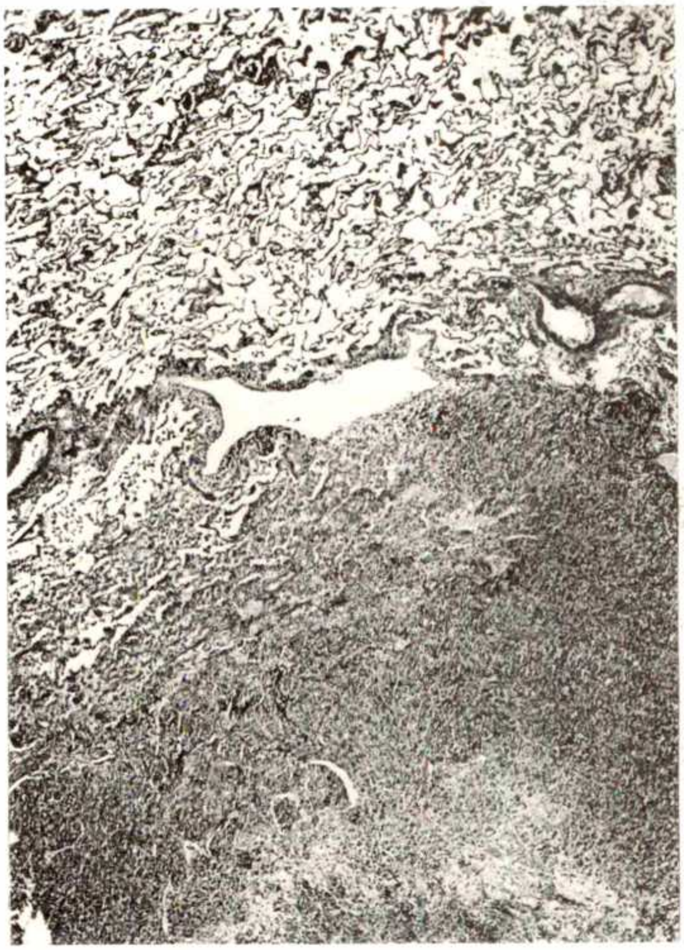

FIG. 4. Photomicrograph of the solitary pulmonary metastasis with adjacent normal lung tissue (x35).

minished to 3mm in diameter and the small tumors had disappeared. The patient felt well until 8/5/73 when she developed fever and abdominal pain. Examination on 8/10/73 revealed ascites and a soft, tender pelvic mass. Chest x-ray was negative (Fig. 5). Exploration on 8/12/73 revealed 3.5 L of ascitic fluid and a hemorrhagic metastasis to the right ovary which weighed 3 kg. No other disease was found, and a bilateral salpingo-oophorectomy was performed with complete resection of the greater omentum. Postop recovery was rapid. The patient did well

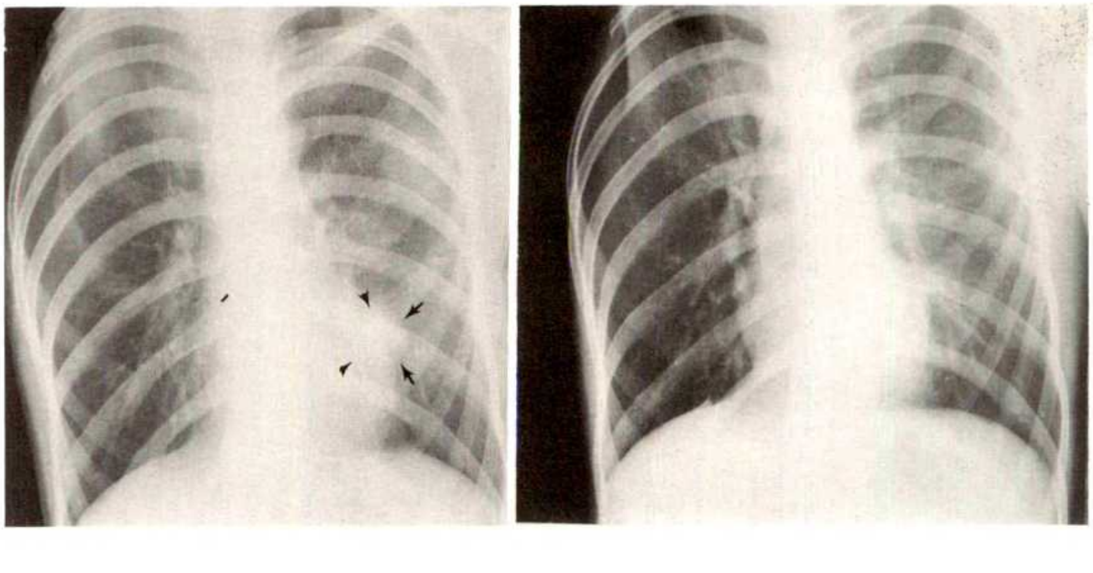

FIG. 5. X-rays showing the resolution of a large left pulmonary metastasis during treatment with Endoxan. (Left, taken on 5/3/73 and right, on 8/6/73)

until 9/4/73 when a repeat chest x-ray showed at least three large tumors in the left lung. The back lesion which had remained at 3 mm since cobalt therapy began to enlarge. Some ascites was noted as well as left leg edema. Adriamycin administration was begun on 9/13/73. After two weeks, with the tumors expanding very rapidly, the Adriamycin was discontinued and Endoxan resumed at 200 mg/day. This was stopped on 10/5/73 after 2 gm because of hematologic depression. The back tumor had stopped growing and the ascites and leg edema had resolved. The pulmonary lesions resolved.

Hospitalization was necessary again on 10/30/73 for rapidly expanding tumors on the back. These tumors were surgically resected and the patient was again well. She received another 5 gm of Endoxan in November. On 12/5/73, a new 2 cm tumor appeared on the back. Endoxan was resumed but the tumor grew slowly and by 1/3/74, two new lesions were present. These were again resected. Multiple small tumors appeared on the right upper back on 1/30/74. With the tumor growing extremely rapidly, the skin and subcutaneous tissue of the right back were resected on 2/5/74. The wound was covered with irradiated skin from another donor. Ten days following that procedure, multiple tumors appeared at the periphery of the skin grafts and new left pulmonary lesions were present. These tumors grew faster than any previously. Combination chemotherapy with 5-FU, Methotrexate, and Endoxan was started on 3/4/74. There was no response after two weeks and it was stopped. By 3/17/74 both lungs were nearly replaced by tumor. There was a rapid downhill course with the patient dying of respiratory insufficiency on 3/26/74. No autopsy was performed.

Discussion

The absence of previous reports of metastatic cystosarcoma phylloides in adolescents would suggest that the disease behaves in a more benign fashion in the young. However, this 14-year-old girl had one of the most aggressive malignant tumors imaginable.

This rapidly progressive course contrasts with the malignant cases previously reported which were generally more indolent. Fifty-eight patients in Kessinger's series[6] were reported dead of metastases at an average of 30 months after initial therapy. The doubling time of approximately 3-5 days seen in most of this patient's recurrences and metastases is among the most rapid described.

In spite of the rapid growth and spread, there was never any documented lymphatic dissemination of this tumor. Recurrent and metastatic cystosarcoma phylloides tumors are essentially always composed of the stromal elements alone. This is the sarcomatous part of the tumor which probably explains the low incidence of lymphatic spread (less than 15% of cases with metastases).[3,6,18,19] Similarly to other sarcomas, most metastasize by the hematogenous route. Involvement of nearly all internal organs has been reported but the lungs are most commonly the site of spread (66% in Kessinger's series).[6]

Perhaps because of this very rapid division of cells, this patient's tumor showed a dramatic initial response to chemotherapy (Fig. 5) and later to irradiation. We are unaware of any previously reported responses to either chemotherapy or irradiation in metastatic cystosarcoma phylloides. Trials have been very few, however. Chemotherapeutic agents tried previously without apparent effect have been: combination nitrogen mustard, 5-FU, and Thiotepa,[4] Endoxan,[15] Actinomycin D,[21] Cyclophosphamide with Methotrexate.[6] This young woman's tumor behaved more aggressively with each recurrence and was unresponsive to the third course of chemotherapy.

From prior reports it is apparent that controlling the primary tumor is of utmost importance. Kessinger[6] found local recurrence in 51% of metastatic cases. In this case, metastasis only became apparent subsequent to the second chest wall recurrence. Considering the rate at which this tumor grew, one could suspect that metastasis did not occur until the first or probably the second recurrence.

This tumor demonstrated unusual malignancy. This report is not proposing routine use of radical operative procedures in all cases. It does emphasize that malignant cystosarcoma phylloides must be respected as a potentially metastasizing, lethal tumor in any age group. The importance of a proper diagnosis and treatment from the onset is obvious.

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Arterial Stenosis Complicating Renal Allotransplantation in Man:

A Study of 38 Cases

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Of 306 renal transplantations, stenosis of the artery supplying the grafted kidney was found in 38 patients three months to two years after they had undergone renal transplantation. The diagnosis was made by arteriography done because of refractory hypertension with or without impaired renal function in 36 patients and as a routine investigation in two normotensive patients. The stenosis was corrected surgically in 14 patients, with resultant lasting relief of hypertension in ten patients and improvement of renal function in five out of six patients with impaired renal function. Different types of stenosis were recognized: stenosis of the recipient artery, stenosis of the suture line, stenosis of the donor renal artery (segmental or diffuse) and multiple forms. The most frequent site of stenosis was the donor artery. There seems to be no single cause of stenosis: atheroma of the recipient vessels, faulty suture technique, hemodynamic disturbances, trauma to donor or recipient arteries account for some cases, whereas in other cases the evidence points to an immune mechanism. This complication of renal transplantation may be more frequent than is thought at present; therefore, routine renal arteriography should be performed at repeated intervals in all transplanted patients.

STENOSIS OF THE ARTERY supplying the grafted kidney is a well recognized complication of human renal allotransplantation. It may cause hypertension with or without impairment of renal function, and these may be permanently relieved by surgical correction of the stenosis. Successful correction has been reported by several workers.[1,3–7,9,12,13]

Experience of arterial stenosis after kidney transplantation during a 16-year period at Professor Hamburger's clinic in Paris, France, is described in this paper. Surgical correction has been performed in 14 patients, and a coordinated study of arteriographic, surgical, and histologic findings has been done. This is one of the largest single published series of surgical corrections of this complication.

Clinical Data

Of 306 renal transplantations performed in 287 patients from June 1959 through December 1973, arterial stenosis has developed in 38 (12.4%), in eight (5.8%) of 137 transplants from related living donors, and in 30 (17.7%) of 169 transplants from cadaver donors. Arterial stenosis appeared in seven patients in whom the donor renal artery had been anastomosed end-to-side to the recipient common iliac artery, and in 31 patients in whom the donor renal artery had been anastomosed end-to-end to the recipient hypogastric artery.

No correlation was found between the time of renal ischemia or the frequency and intensity of early rejection crises on the one hand, and the frequency of arterial stenosis on the other hand.

Blood Pressure

Hypertension was defined as a diastolic blood pressure of more than 100 mm Hg obtained at not less than three consecutive readings.

Of the 38 patients with arterial stenosis, the blood pressure before transplantation had been normal in 12 patients and elevated in 26 patients.

In two of the 12 patients who had been normotensive before transplantation, the blood pressure remained normal, despite the development of arterial stenosis. In the remaining ten patients, hypertension was noted between three months and two years, but most often about six months, after transplantation. In some of these patients hypertension developed within a space of 48 hours. In all of the 26 patients who had been hypertensive before transplantation, hypertension persisted or reappeared in the first six months post-transplantation.

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In some of the 36 hypertensive patients, a bruit became audible over the site of the transplanted kidney at approximately the same time that the hypertension became obvious.

In one of the hypertensive patients clinical features suggestive of allograft rejection developed, but there was no response to corticosteroid therapy and the results of the renal biopsy were normal. The correct diagnosis was given by arteriography.

Renin activity in the vein of the transplanted kidney was elevated in two of the 14 patients in whom it was estimated.

Renal Function

Renal function tests (determination of blood urea nitrogen, of blood creatinine concentrations and urinary cell count per minute, and creatinine clearance studies) were performed in all 38 patients.

Impairment of renal function may be attributed to the stenosis alone, only if all abnormalities disappear after correction of the stenosis.

Arteriography

Renal arteriography was done in 36 patients because of hypertension with or without deteriorating renal function, and as a routine investigation in the two patients who had normal blood pressures.

Surgical Procedures

Fourteen patients have been selected for surgical correction of arterial stenosis. The criteria for selection were: 1) hypertension not controllable medically and not due either to the presence of the patient's own diseased kidneys (previous binephrectomy) or to chronic rejection or recurrent glomerulitis (renal biopsy); and 2) increased renin activity in the vein of the transplanted kidney. Mild or moderate impairment of renal function was not a contra-indication to correction of the stenosis provided arteriography and renal biopsy could rule out a recurrent glomerulitis or a serious rejection process.

Surgical correction has been performed in these 14 patients. The intervals between transplantation and correction ranged from six months to two years. Correction was effected by resection of the stenotic area and reimplantation of the renal artery into the common iliac artery in four patients (direct in one and by saphenous vein autograft in three); by resection of the stenotic area and end-to-end renal artery-hypogastric artery reanastomosis in eight patients (direct in six and with interposition of a saphenous vein autograft in two); and by venous patch angioplasty in two patients. Patch angioplasty was used only when the stenosis was due to faulty technique and confined to the suture line and both arteries were healthy.

In the 11 cases in which the pathologic portion of artery was resected, the sections of artery removed were examined histologically. Two of the sections were also examined by an immunofluorescence technique.

In 24 patients surgical correction of the stenosis was not indicated: two patients had neither hypertension nor impaired renal function; in 15 patients hypertension was satisfactorily controlled by hypotensive drugs and a low-sodium diet; and in seven patients uncontrollable rejection reactions required transplant nephrectomy.

Clinical Results

Mortality

One patient died from brain damage on the fourth day after operation for stenosis. At the time of operation he was already in deep coma due to malignant hypertensive encephalopathy.

Blood Pressure

The blood pressure fell to normal levels immediately after operation in all of the 14 patients who underwent correction of the stenosis.

In ten of the 13 surviving patients the blood pressure has remained normal since operation. The ten include two in whom postoperative arteriography showed evidence of chronic rejection, and a third whose transplanted kidney had to be removed three months after correction of the stenosis because it had become affected by the original renal disease. There was no correlation between pre-correction renin activity in the vein of the transplanted kidney and post-correction fall in blood pressure.

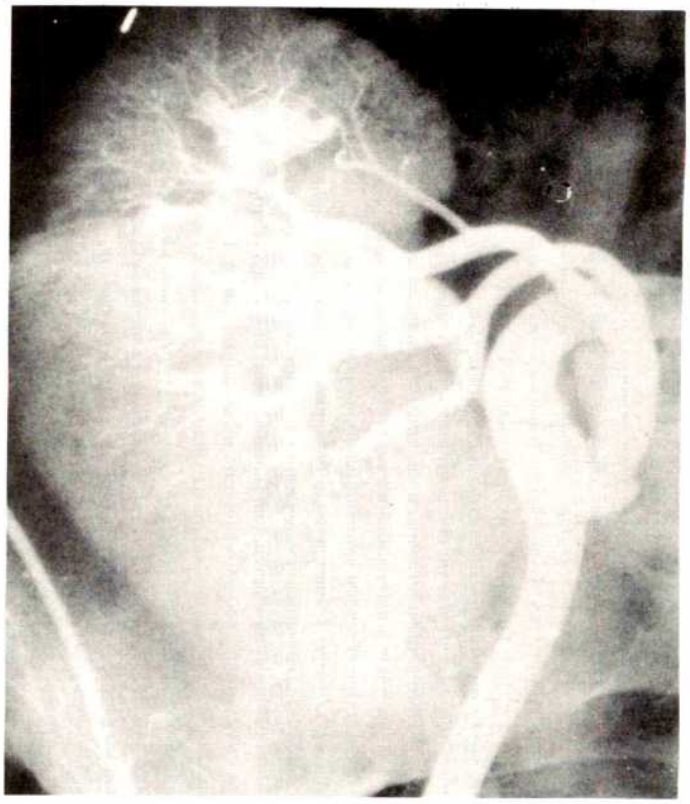

FIG. 1. Renal transplant. Stenosis has developed at the origin of the recipient hypogastric artery.

Hypertension associated with chronic rejection reactions reappeared in three patients: two patients still have slight hypertension that is satisfactorily controlled medically; in the third patient hypertension due to chronic rejection with destruction of the allograft led to removal of the transplanted kidney 18 months after correction of the stenosis.

Renal Function

Of six patients with impaired renal function at the time of correction of the stenosis, renal function became normal during the days immediately following operation in five. The sixth patient had a chronic rejection reaction and his renal function remained unchanged after operation.

In seven patients renal function was normal before operation and remained normal after operation.

Recurrence

At the present time, in no case, has arterial stenosis recurred.

Pathological Results

Classification

The following morphological and topographical classification is based upon arteriographic and operative findings in 14 patients, and on arteriographic findings only in the remaining patients. The types of arterial stenosis identified by us might serve as a basis for future studies of this condition.

The following types of stenosis were recognized.

Stenosis of the Recipient Hypogastric Artery (Fig. 1). This was usually due to atheromatous changes in that vessel with, in some cases, flexion at an acute angle of the hypogastric artery over an atheromatous plaque.

Stenosis of the Suture Line between the recipient and donor vessels (Figs. 2 and 3): a faulty suture technique is responsible for this type of stenosis.

Stenosis of the Artery of the Transplanted Kidney. Here, two major types of stenosis, the localized and the diffuse, were distinguished:

1) Localized Stenosis. The length of the stenotic zone did not exceed 8 mm and the portions of artery and/or the arterial branches situated on either side of the stenosis were of normal consistence and caliber. This type of stenosis may be *proximal*, that is, situated just beyond the suture line but in contact with it (Fig. 4), or *distal*, that is, at a distance from the suture, near the bifurcation of the renal artery (Fig. 5) or even affecting the bifurcation itself or the branches.

2) Diffuse Stenosis. This consisted of a tubular narrowing of the entire length of the donor renal artery, the suture line being spared (Fig. 6). On arteriograms the outline of the stenosed artery was frequently irregular and the appearances suggested extensive endothelial proliferation. At operation the reduced external caliber of the donor artery contrasted with the normal caliber of the recipient artery, recalling renal artery atresia.

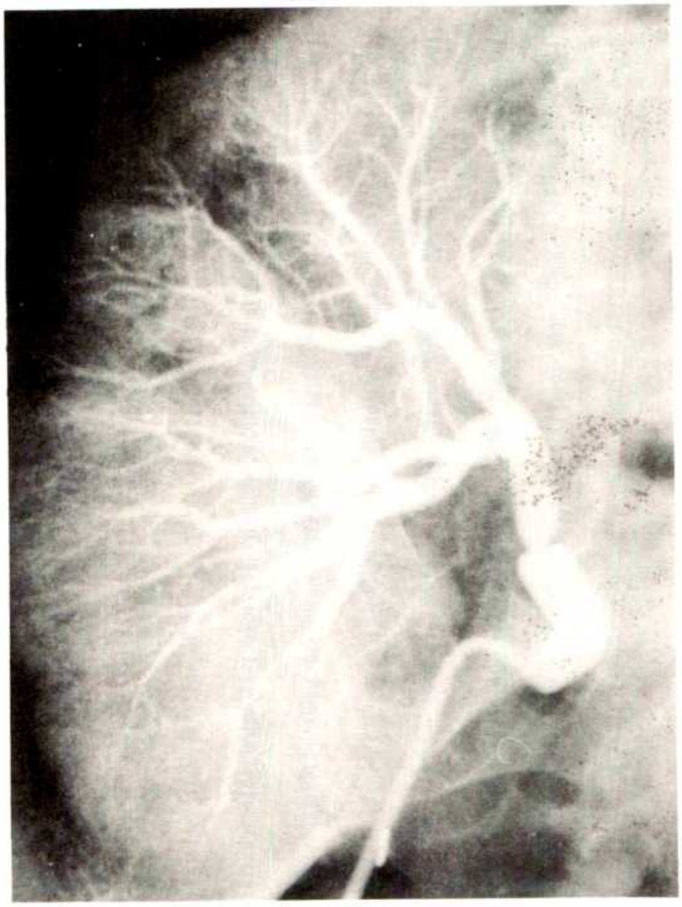

FIG. 2. Renal transplant. Stenosis at the suture line in end-to-end hypogastric artery-renal artery anastomosis.

Histologic examination of the resected arterial segments showed, in all cases of stenosis of the transplant artery, fibrous endarteritis with severe intimal thickening sparing the suture line. Immunofluorescence revealed complement in the vessel wall near the stenosed area in the two cases in which this technique was used.

Multiple Stenoses (Fig. 7). These associate two or more stenotic sites of the different varieties described just before.

In the operated cases, where the angiographic and operative findings leave no doubt about the exact site of the stenosis, the most frequent site was the donor renal artery: ten of 14 operated patients as compared to two stenoses of the recipient artery and two at the suture line. In the non operated patients, if it be assumed that the sites of stenosis as indicated by arteriography alone were correct, the most frequent site was the donor artery too.

Discussion

The true incidence of posttransplantation arterial stenosis has been underestimated until now, because, in no series, has routine renal arteriography of all transplanted patients at repeated intervals been performed.

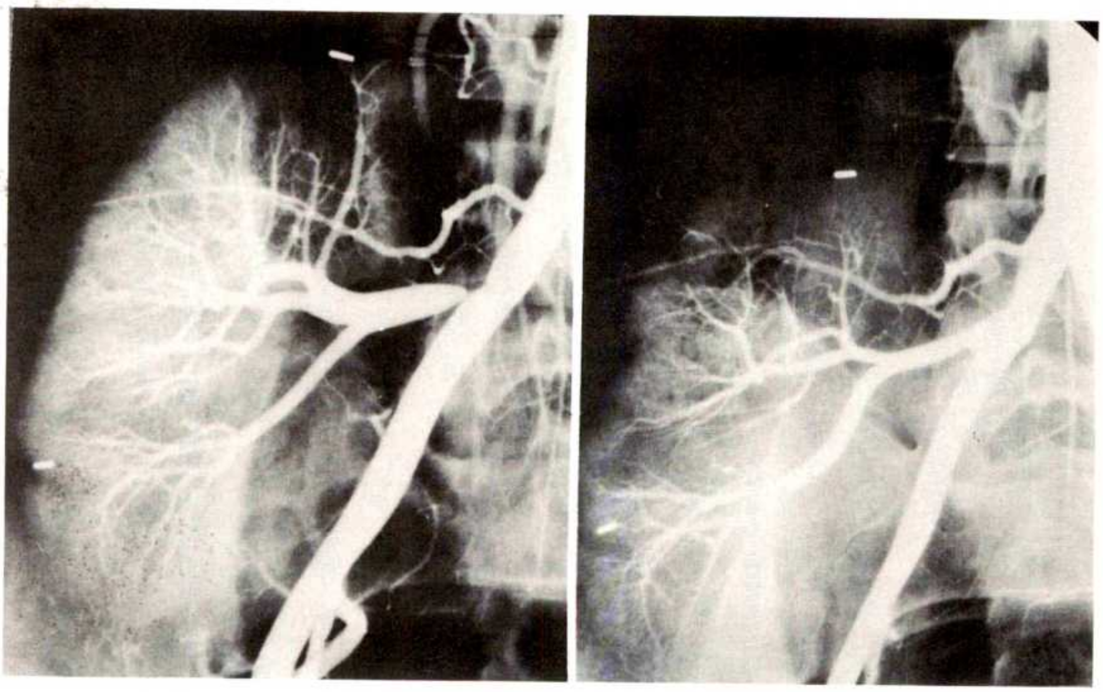

FIG. 3. Renal transplant. (Left) Stenosis at the suture line in end-to-side common iliac artery-renal artery anastomosis. (Right) Arteriogram after venous patch angioplasty for correction of the stenosis.

Incidences of 15 of 155 transplantations (9.7%)[6] and five of 118 transplantations (4.2%)[12] have been reported. The incidence in our series, 38 cases in 306 transplants, or 12.4%, probably does not reflect the actual frequency of this complication. Routine angiographic studies were undertaken in our 100 most recent transplant patients only, 23 of whom showed evidence of arterial stenosis; in some cases, arteriography was done during the early posttransplantation phase only, before roentgenologically visible stenosis could have developed. If the two normotensive patients had not undergone routine arteriography their stenosis might never have been detected. Renal arteriography at regular intervals in all kidney transplant patients, irrespective of the presence of hypertension, might well reveal an incidence of arterial stenosis as high as 25%.

The importance of arteriography in posttransplantation arterial stenosis is not only statistical. It is also diagnostic, especially in those atypical cases in which, as in one of our patients, the clinical picture brings to

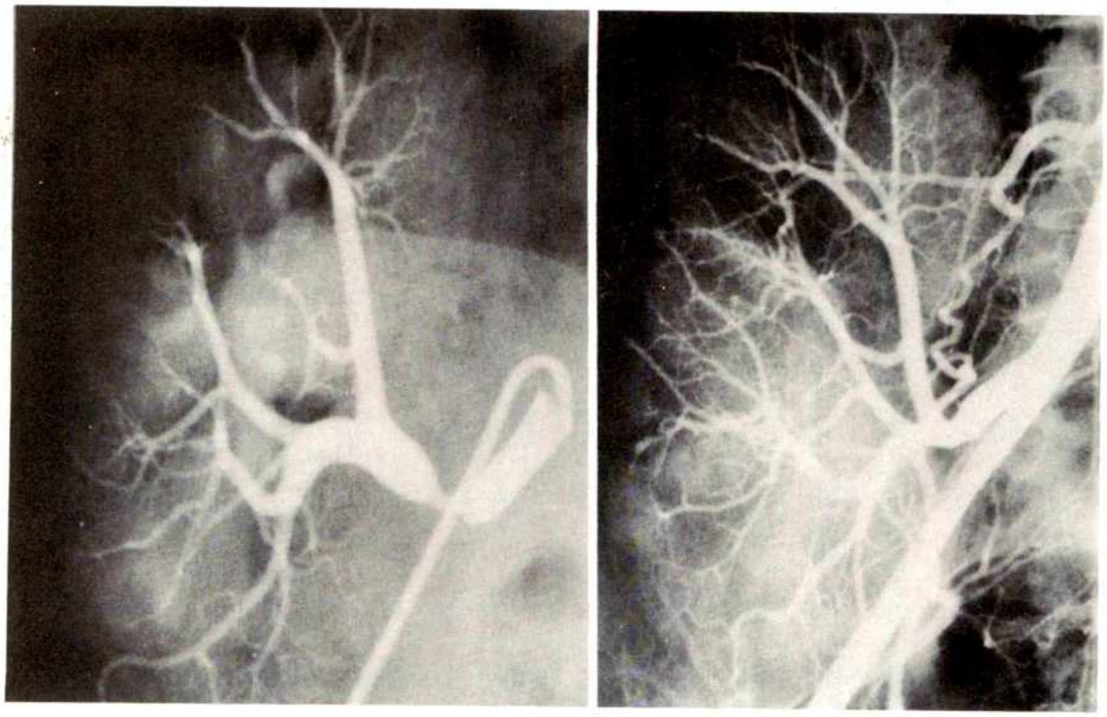

FIG. 4. Renal transplant. (Left) Proximal type of stenosis of donor renal artery. The stenosis is just beyond the suture line, but in contact with it. (Compare with Fig. 2.). (Right) Arteriogram after resection of the stenosis and end-to-end reanastomosis.

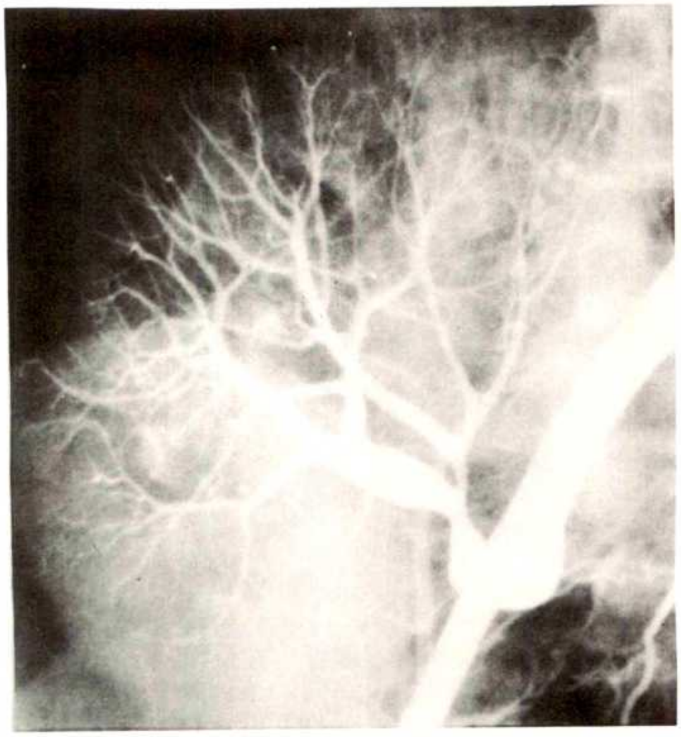

FIG. 5. Renal transplant. Distal type of stenosis of donor renal artery. The stenosis is near the bifurcation of the artery.

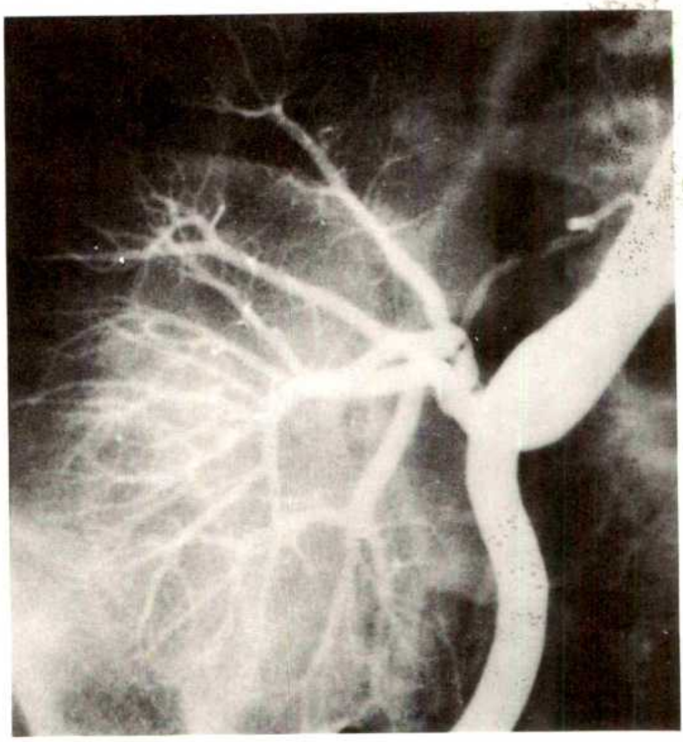

FIG. 7. Renal transplant. Multiple areas of arterial stenosis.

mind that of a rejection crisis. Simmons et al.[11] have reported two patients in whom renal artery stenosis completely simulated intractable allograft rejection. Arteriography gave the correct diagnosis and, thanks to surgical correction, the kidneys were salvaged. Otherwise, transplant nephrectomy would have been done. We differ from the view expressed by Smellie et al.[12] that it is unnecessary to do posttransplantation arteriograms for the investigation of hypertension unless an arterial bruit is audible over the transplant. Such bruits have not, in our experience, constantly accompanied arterial stenosis. The contribution of arteriography in the elucidation of the complications of renal transplantation has been well described by Staple and Chiang.[13] In our view it should be performed during the first month after renal transplantation, and again six months and two years after transplantation.

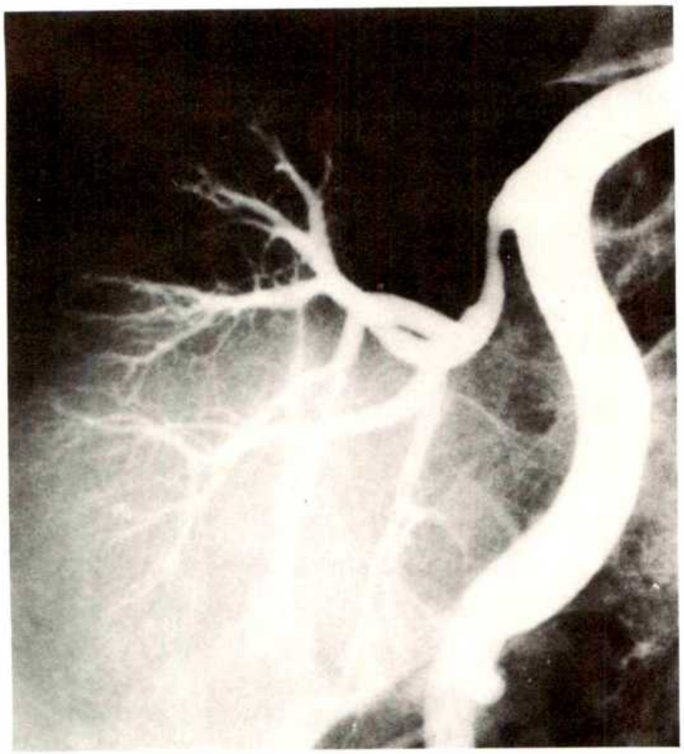

FIG. 6. Renal transplant. Diffuse stenosis of the entire trunk of the donor renal artery.

Several explanations for the development of arterial stenosis after kidney transplantation have been advanced.

Atheroma of the transplanted patient is a cause of stenosis of the recipient artery. The vessels should be carefully scrutinized for atheroma and if atheromatous plaques exist in the hypogastric artery, either endarterectomy should be performed before anastomosis or a different recipient artery should be used.

Faulty suture technique, such as excessively broad suture bites, the use of extra stitches, or mechanical "tucking" of one or both arteries, produces localized stenosis confined to the suture line. Suture errors are especially liable to occur in end-to-end anastomoses because a gross difference in texture and caliber between the donor and the recipient vessels exists frequently.

Traumatic causes include: damage to donor or recipient artery, either during removal of the donor's kidney or during transplantation, by traction, clamping or snaring; endothelial lesion or subintimal dissection by the perfusion cannula. Trauma does not explain satisfactorily all cases of stenosis, as it is difficult to see how it could cause stenosis of a single branch of the renal artery or diffuse narrowing of the whole renal arterial tree whose radiographic appearance is similar in all cases.

Disturbed hemodynamics in end-to-side anastomosis is held responsible for stenosis by Morris et al.[5] Stenosis, according to these workers, may result from an over acute angle of take-off between the donor renal artery and the iliac vessel, or when a redundant renal artery leads to kinking with consequent turbulent flow. Only seven of our own patients had had end-to-side anastomosis, as compared to 31 in whom it had been end-to-end.

An immune causative factor has been advanced as a cause of stenosis of the transplant's artery (Kincaid-Smith et al.,[2] Porter et al.[10]). The principal arguments in favor of an immunologic cause are: 1) the similarity between the histologic changes in the stenosed arteries and the vascular lesions of renal allograft rejection, namely, subintimal fibrosis and intimal proliferation; and 2) the existence of privileged cases where vascular lesions of allograft rejection, with identical histologic appearance, affect the whole arterial tree from the main renal artery to the renal capillaries. The first stage in the process seems to be deposit of fibrin and platelets on the endothelium, leading to endothelial proliferation and intimal fibrosis. O'Connell and Mowbray[8] produced intimal thickening in rabbit arteries by exposing the arterial endothelium to xeno- and allo-antibodies. The presence of complement in the stenosed arterial walls in two of our patients may support the immunological explanation.

Whatever the cause, histologic examination of resected stenotic arterial sections alone can give no clue to the mechanism of production of the stenosis; because of the time interval between the triggering mechanism and operation, all that is seen is organized cicatricial fibrosis. But the association with changes in the intrarenal capillaries that are characteristic of rejection supports an immune mechanism.

The non-recurrence of stenosis in our patients, contrasting with the experience of Lee et al.,[3] may be due to our practice of resecting diseased arterial tissue. We have invariably sutured healthy artery to healthy artery, and have reserved patch angioplasty for stenosis restricted to the line of anastomosis.

In the presence of hypertension with or without deterioration of renal function not ascribable to causes other than arterial stenosis and not yielding to medical treatment operation should be recommended. The role of the stenosis in generating hypertension is borne out in our series by the facts that 1) ten of our patients did not become hypertensive until after transplantation, 2) in two patients removal of their own diseased kidneys did not relieve hypertension, which persisted until the stenosis was corrected, and 3) renin activity in the vein of the transplant kidney was elevated in two patients.

The renal impairment was thought to be due to renal ischemia in five of our patients: this was suggested in these cases by the fact that a reduction in blood pressure obtained by medical therapy before correction of the stenosis led to further deterioration of renal function. The renal ischemia in its turn was secondary to the stenosis as was shown by the reversion to normal renal function immediately after correction of the stenosis.

Although elevated renin activity in the vein of the transplanted kidney is an indication for operation, a normal level of renin activity is neither a contraindication to operation nor an unfavorable prognostic factor, since it does not influence the hypotensive effect of surgical correction.

Perhaps long-term anticoagulant therapy, as suggested by Kincaid-Smith et al.[2] will reduce the frequency of this complication of renal allotransplantation.

Such vascular lesions may conceivably be encountered after transplantation of other organs and account for some secondary failures, especially of heart transplants.

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Factors Determining Successful Liver Preservation for Transplantation

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Auxiliary liver allotransplants will survive for relatively long periods of time after 24 hour hypothermic (10–12C), pulsatile perfusion. The best perfusate was a silica gel fraction of dog plasma with added potassium chloride gel made hyperosmolar with glucose. Further improvement could be achieved with added allopurinol and methylprednisolone. Nonpulsatile flow or lower temperatures were less effective preservation techniques.

ALTHOUGH the *in vitro* storage of kidneys for transplantation is now routine, preservation of the liver by similar techniques has been limited to a few hours.[2,26] Belzer[2] has noted endothelial damage and sinusoidal disruption after 10 hours of hypothermic perfusion. Impairment of mitochondrial functions, specifically the oxidative phosphorylation, the respiratory control and the capacity to oxidize substrates are also commonly observed after short periods of either normothermic or hypothermic perfusion.[7,24] Attempts to maintain the viability of the organ by means of vascular perfusion and oxygenation have frequently failed.[2,4,26] The use of continuous pulsatile perfusion[27,36] plus hyperbaric oxygen have only partially improved the preservation of liver homografts.[5,32]

In previous experiments utilizing hypothermic plasma perfusion of the kidney and small intestine we have developed several techniques[37,41] which permit preservation for very long periods. These include modifications[37,39] and additives[38,42] to the plasma perfusate as well as modifications in pressure and flow.[38,39,41,42] The present study was designed to study these and other modifications in attempting to prolong the survival of dog livers *in vitro* prior to auxiliary allotransplantation.

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Materials and Methods

Adult unrelated mongrel dogs of either sex underwent auxiliary liver transplantation according to a modified technique of Bengochea-Gonzalez and associates.[3] Recipient animals weighed 19-29 kg and donor dogs weighed 8–14 kg. All animals were anesthetized with sodium methohexital for induction and Fluothane for maintenance. Oxygen was used during ventilation. Ringer's lactate was given intravenously during surgery. Isoproterenol HCL 1:5000 (0.2 mg) and heparin (500 U/kg) were administered intravenously 20 minutes before the graft was removed from the donor.

The liver graft was removed from the donor dog with attached long segments of supra and infra-hepatic vena cava, portal vein and celiac axis. The donor's liver was flushed through the celiac axis and portal vein with cold (4C) Ringer's lactate solution containing heparin (10,000 U/L) and procaine (1 gm/L), until the venous effluent was clear. Usually 2 L of flushing solution was utilized for a complete washout.

Immediately after flushing, the liver was preserved by hypothermic perfusion for 24 hours (Figs. 1 and 2) except the livers of dogs from Group I which were transplanted immediately. The livers of dogs in Group II were perfused with cryoprecipitated plasma (CPP) prepared according to standard techniques.[1] The livers of dogs in group III were perfused with a silica gel fraction (SGF) of plasma recently described by our group.[37] SGF is basically a plasma fraction treated with silica gel resulting in removal of all cholesterol and fibrinogen and most of the lipoproteins.[37] Both CPP and SGF have a normal concentration of extracellular electrolytes (sodium 140 mEq/L, potassium 4.0 mEq/L), and osmolarity (290 mOsm/L) with total proteins of 4.0 gm% and

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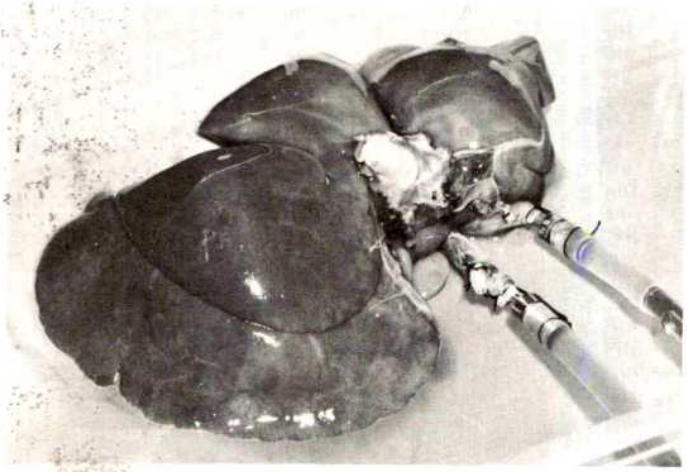


FIG. 1. Canine liver being perfused through the celiac axis and portal vein. The common bile duct is cannulated and the bile collected outside the perfusion cassette. Perfusate comes out the superior and inferior vena cava and recirculates again into the system.

albumin 2.9 gm%. The livers of dogs from Group IV to VII were perfused with SGF to which KCL, dextrose and salt poor human albumin (Hyland, Travenol Laboratories, Costa Mesa, Calif.) had been added (MSGF). The final concentration of these additives in the perfusate was K +100 mEq/L, glucose 1050 mg/L, total proteins 5.0 gm%, albumin 3.7 gm%, and osmolarity 560 mOsm/L. Additives to all perfusates included phenolsulfonphthalein (PSP) (2 ml/L), insulin (80 U/L), methylprednisolone (800 mg/L), and ampicillin (1 gm/L).

The perfusion system consisted of a Mox-300 machine (Waters Instruments, Inc., Rochester, Minn.) that was primed with 1800 ml of the perfusate maintained at 10–12C, pH 7.35 (10C), pO_2 800 mmHg. The livers were perfused through the celiac axis or hepatic artery with a systolic perfusion pressure of 60 mmHg, pulse rate 60/min, and through the portal vein by means of gravity flow (12 cm H_2O) (Figs. 1 and 2). The bile was continuously obtained from a catheter placed in the common bile duct. Perfusate flow and pressure were periodically determined until the end of preservation. During perfusion, samples were taken from the perfusate every two hours for the first six hours, then every six hours until the end of perfusion. Electrolytes, osmolarity, pH, pO_2, pCO_2, glucose, alkaline phosphatase, lactic acid dehydrogenase (LDH), glutamic oxaloacetic transaminase (GOT), β-glucuronidase, lactic acid, bilirubin and ammonium were determined in all samples (Bilirubin, LDH, and SGOT were determined according to the techniques of Bio-dynamics Inc., Indianapolis, Ind. Lactic acid was obtained from Sigma Chemical Co., St. Louis, Mo., and ammonia from Hyland, Travenol Laboratories, Costa Mesa, Calif.

Following 24 hours of perfusion, the liver was reflushed

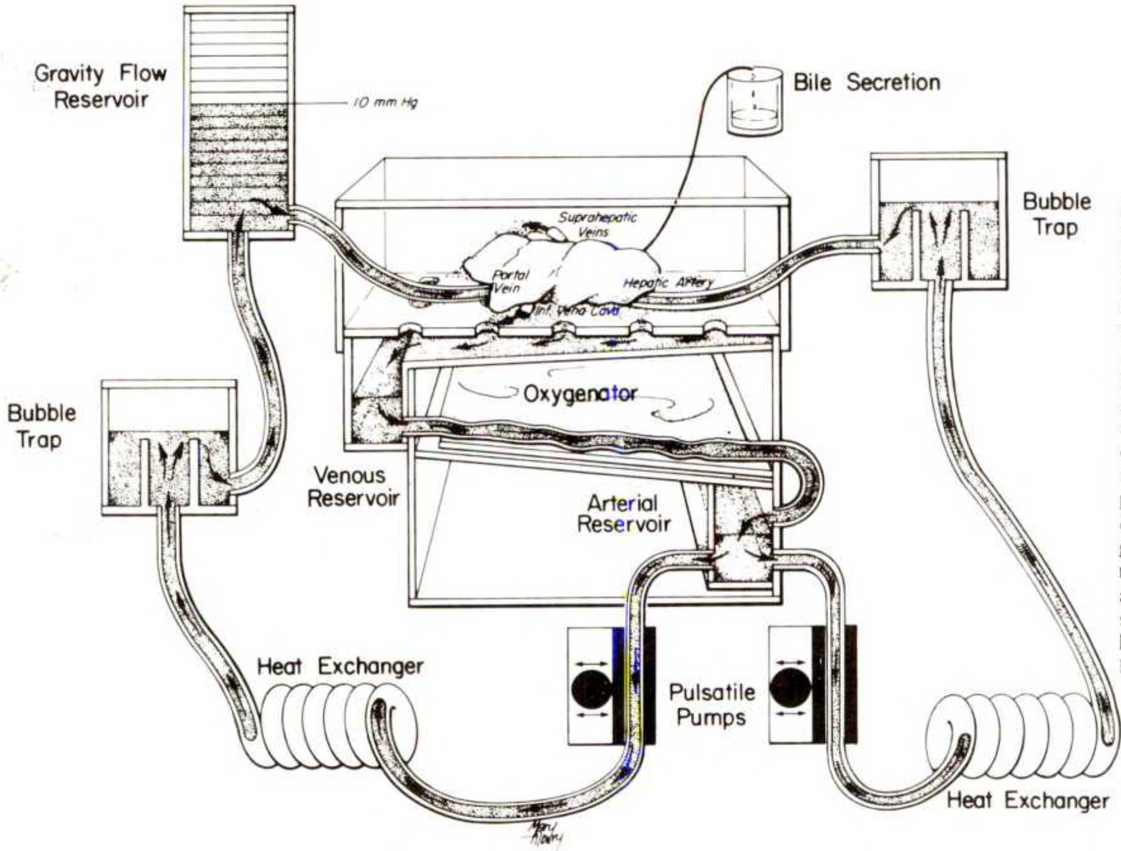
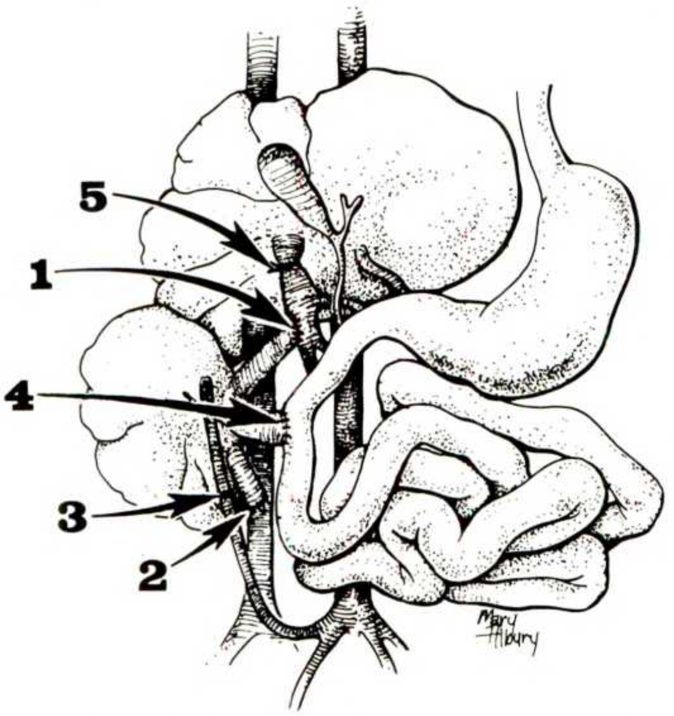


FIG. 2. Diagram of the liver perfusion system. The liver is perfused through the hepatic artery or celiac axis with pulsatile flow (60 mmHg) and through the portal vein with gravity flow (12 cm H_2O). The perfusate comes out both vena cava and circulates through the oxygenator (pO_2 800 mmHg), arterial reservoir, pulsatile pumps and heat exchanger. The flow that goes to the portal vein is derived in a gravity fashion and the arterial flow in a pulsatile modality. Bile is collected from the common bile duct.



1 Portal vein - portal vein anastomosis.

2 Inferior vena cava - Inferior vena cava anastomosis.

3 Celiac axis - right external iliac anastomosis.

4 Cholecysto — duodeno anastomosis.

5 Portal vein ligated.

FIG. 3. Technique of auxiliary liver transplantation. The portal vein was ligated in the host's liver (5), and the splanchnic flow was directed to the transplanted liver through an end-to-end portal to portal anastomosis (1). The celiac axis and inferior vena cava anastomosis were performed end-to-end to the right external iliac artery and end-to-side to inferior vena cava respectively (2,3). A cholecysto-duodeno anastomosis was performed (4).

through the portal vein and the hepatic artery with a total of 1 L of cold (4C) Ringer's lactate to wash out the excessive K + before auxiliary transplantation into an unrelated recipient animal. The donor liver was continuously flushed with this solution while being transplanted. It was placed in the right side of the abdomen with its hilum towards the midline. Two end-to-side venous anastomoses were performed: portal vein to either superior mesenteric vein or portal vein of the recipient and inferior vena cava to infrarenal vena cava. One end-to-end arterial anastomosis was done, celiac axis of the donor to right common iliac of the recipient. The recipient's portal vein was then ligated to direct host splanchnic blood flow into the auxiliary liver. A side-to-side, one layer cholecystoduodeno anastomosis completed the operation (Fig. 3).

After transplantation the dogs were treated with intravenous Ringer's lactate to which dextrose 50% (50 ml/L), salt poor albumin 25% (50 ml/L), multivitamins (2 ml/L) and potassium chloride (20 mEq/L) were added. Chloramphenicol 500 mg intravenously twice a day and kanamycin 500 mg intramuscularly every 12 hours were given for three days after surgery. Oral feeding was started progressively at the 5th postoperative day. All dogs were treated with azathioprine 5 mg/kg/day for the first three days and then 2.5 mg/kg/day until death. Such an immunosuppressive regimen will not normally prolong the survival of nephrectomized kidney allograft recipients in dogs.[40] Blood samples were obtained from recipients daily for two weeks, and twice a week thereafter for: hemoglobin, hematocrit, leukocyte count, electrolytes, lactic acid, bilirubin, alkaline phosphatase, LDH, SGOT, and ammonium.

Weekly ^{99m}Tc-pertechnatate and ^{131}I rose bengal gamma scanning were obtained. Postmortem examination was performed in all animals. Biopsies from both livers were taken weekly and final microscopic study was performed at

TABLE 1. *Perfusion Characteristics During Liver Preservation for 24 Hours (Mean Values ±SE)*

Group	Perfusate	Flow Rate (ml/min/gm) I	Flow Rate (ml/min/gm) F	Weight Gain (%/24 hrs)	Fluid Loss (L/24 hrs)	Bile Production (ml/gm tissue/24 hr)
II	CPP	0.6±0.1	0.5 ± 0.1^{a}	$21.8 \pm 4.5^{b,c}$	$0.5 \pm 0.1^{b,c}$	$0.2 \pm 0.06^{c,e}$
III	SGF	0.7±0.1	0.8±0.2	17.3±5.1	0.3±0.1	0.3 ± 0.08^{e}
IV	MSGF	0.8±0.1	0.9±0.2	10.1 ± 3.5^{c}	$0.2 \pm 0.1^{c,d}$	0.4 ± 0.1^{e}
V	MSGF with Gravity flow	0.8±0.2	0.6 ± 0.1^{a}	20 ± 8.5^{b}	0.4 ± 0.2^{b}	$0.04 \pm 0.01^{b,e}$
VI	MSGF with temperature at 7 C	0.7±0.2	0.6 ± 0.1^{a}	17 ±6.2	0.5 ± 0.1^{d}	$0.2 \pm 0.05^{d,e}$
VII	MSGF with methylprednisolone and allopurinol	0.8±0.1	1.1 ± 0.2^{a}	8.6 ± 3.5^{b}	$0.1 \pm 0.05^{b,d}$	$0.5 \pm 0.1^{b,d,e}$

I = Initial
F = Final

[a] $p<0.05$ when final values of Groups II, V, VI were compared to final values of Group VII.
[b] $p<0.05$ when values of Groups II, V were compared to values of Group VII.
[c] $p<0.05$ when values of Group II were compared to values of Group IV.
[d] $p<0.05$ when values of Group VI were compared to values of Groups IV, VII.
[e] $p<0.05$ when values of Group V were compared to the values of Groups II, III, IV, VI, VII.

TABLE 2. *Perfusate Concentration During Liver Preservation for 24 Hours (Mean Values ±SE)*

Group	Perfusate	Lactic Dehydrogenase (U/100 ml)		SGOT (U/100ml)		Glucose (mg%)		Osmolarity (mOsm/L)	
		I	F	I	F	I	F	I	F
II	CPP	$12 \pm 4.5^{a,b}$	$95 \pm 12.3^{c,d}$	80 ± 18^{a}	413 ± 96^{d}	350 ± 42^{g}	295 ± 27^{h}	285 ± 10^{g}	292 ± 8^{h}
III	SGF	15 ± 5.0^{a}	61 ± 9.6^{c}	64 ± 10^{a}	396 ± 85^{f}	288 ± 66^{g}	235 ± 61^{h}	288 ± 9^{g}	295 ± 12^{h}
IV	MSGF	19 ± 4.2	32 ± 8.5^{c}	75 ± 33^{e}	305 ± 135	1050 ± 45^{g}	928 ± 85^{h}	580 ± 26^{g}	545 ± 31^{h}
V	MSGF with gravity flow	$28 \pm 6.5^{a,b}$	$315 \pm 42^{c,d}$	85 ± 28^{a}	298 ± 86	935 ± 72^{g}	1038 ± 86^{h}	535 ± 63^{g}	515 ± 31^{h}
VI	MSGF with temperature at 7 C	15 ± 4.3^{a}	$195 \pm 31.2^{c,d}$	68 ± 14^{a}	347 ± 43^{d}	975 ± 83^{g}	1076 ± 72^{h}	508 ± 47^{g}	480 ± 23^{h}
VII	MSGF with methylprednisolone and allopurinol	23 ± 3.5^{b}	47 ± 14.9^{d}	53 ± 18^{e}	$164 \pm 39^{d,f}$	1012 ± 46^{g}	957 ± 63^{h}	547 ± 3.5^{g}	536 ± 19^{h}

I = Initial
F = Final

[a] $p < 0.05$ when initial and final values were compared in Groups II, III, V, VI
[b] $p < 0.05$ when initial values of Group II were compared to initial values of Groups V, VII
[c] $p < 0.05$ when final values of Groups II, III, V, VI were compared to final values of Group IV
[d] $p < 0.05$ when final values of Groups II, V, VI were compared to final values of Group VII
[e] $p < 0.05$ when initial and final values were compared in Groups IV, VII
[f] $p < 0.05$ when final values of Group III were compared to final values of Group VII
[g] $p < 0.05$ when initial values of Groups II, III were compared to initial values of Groups IV, V, VI, VII

death. Statistical analysis with standard error and students' T test was determined for all parameters between groups of animals.

Seven groups of five dogs each (35 dogs) were studied. Group I dogs received fresh auxiliary liver transplants without preservation. Group II, the livers were perfused with CPP, group III, SGF as perfusate, group IV, SGF made hyperglycemic, hyperosmolar and hyperkalemic (MSGF), groups V to VII, MSGF was utilized as perfusate with the following changes in the system: group V, gravity flow at 12 cm H_2O was given simultaneously through both the portal vein and celiac axis, group VI, the temperature of the system was decreased from 10-12C, to 7°C, group VII, methylprednisolone 2 gm/L and allopurinol 500 mg/L were added to MSGF perfusate.

Results

Effect of Perfusate Composition, Temperature and Perfusion Technique on Fluid Loss, Flow Rate and the Chemical Composition of Perfusate During 24-hour Preservation of the Liver

Table 1 lists the perfusion characteristics at the start and at the end of the 24-hour period of liver preservation. Comparing the perfusate, the temperature, the pulsatile characteristics of the intra-arterial flow did not result in any significant difference in the flow rate during the start of perfusion. Flow rate remained reasonably stable. There was no significant decrease in flow rate during the entire period of perfusion. In fact, the only major change occurred when MSGF with added methylprednisolone and allopurinol were utilized as plasma perfusate. In this case, the flow rate increased during the 24-hour perfusion. During perfusion, there was a definite increase in the weight of the liver suggesting the formation of edema. In livers perfused with unmodified CPP or SGF or in livers perfused under gravity flow or at 7C, this ranged from 17% to 25% of the initial liver weight. However, when MSGF was utilized for perfusate with pulsatile arterial flow or MSGF with added methylprednisolone and allopurinol, the weight gain ranged only between 8% and 12%. Similarly, the perfusate fluid loss in the MSGF and MSGF with added methylprednisolone and allopurinol group was less than when the unmodified CPP and SGF was utilized or when gravity flow was utilized or MSGF at 7C.

TABLE 3. *Effect of the Modification of Perfusion on the Survival of Dogs With Auxiliary Liver Preserved For Twenty-four Hours*

Groups	Perfusate	Survivors >5 days (#dogs)	Mean Survival (Days ± SE)
I	None	5/5	14.5 ± 3.5
II	CPP	1/5	2.9 ± 1.1
III	SGF	2/5	4.7 ± 1.2
IV	MSGF	4/5	11.7 ± 2.9
VII	MSGF with methylprednisolone and allopurinol	5/5	13.6 ± 4.1

Bile production when MSGF perfusate was utilized at gravity arterial flow was negligible. Bile production of 0.2 ml/gm of tissue occurred from livers perfused with unmodified CPP, SGF, MSGF, or MSGF at 7C. Increased bile production was noted when MSGF or MSGF with methylprednisolone and allopurinol were utilized as perfusates.

Effect of Modifying Perfusate Composition and Perfusate Technique on the Chemical Composition of Perfusate During Liver Preservation for 24 Hours

Table 2 lists changes in perfusate composition which occurred during 24 hours perfusion. Unmodified CPP or SGF resulted in moderate increases in lactic dehydrogenase, SGOT, lactic acid and ammonium, whereas the

TABLE 2. *(Continued)*

Bilirubin (mg%)		Lactic Acid (mg%)		Potassium (mEq/L)		Ammonium (μg%)	
I	F	I	F	I	F	I	F
0.7 ± 0.1	0.9 ± 0.2	14 ± 4.5^{i}	35 ± 8.2	$4.0\pm0.2^{g,k}$	12.5 ± 3.2^{h}	285 ± 42^{a}	825 ± 68^{m}
1.0 ± 0.1	0.9 ± 0.05	18 ± 2.8	31 ± 6.7	$3.9\pm0.3^{g,k}$	8.7 ± 2.6^{h}	$195\pm55^{a,l}$	416 ± 37^{m}
0.6 ± 0.2	0.4 ± 0.1	16 ± 4.5	34 ± 8.5	110 ± 6.5^{g}	115 ± 8.7^{h}	315 ± 45	425 ± 80^{m}
0.5 ± 0.2	0.6 ± 0.3	13 ± 4.2^{i}	54 ± 22.9^{j}	96 ± 8.7^{g}	107 ± 10.5^{h}	322 ± 53^{a}	875 ± 41^{m}
0.3 ± 0.3	0.9 ± 0.1	14 ± 3.9^{i}	37 ± 12.2	87 ± 6.2^{g}	99 ± 8.4^{h}	$387\pm46^{a,l}$	832 ± 63^{m}
0.5 ± 0.1	0.7 ± 0.2	14 ± 4.3	26 ± 10.7^{j}	103 ± 9.7^{g}	105 ± 11.3^{h}	373 ± 63^{l}	575 ± 98

[h] $p<0.05$ when final values of Groups II, III were compared to final values of Groups IV, V, VI, VII
[i] $p<0.05$ when initial and final values were compared in Groups II, V, VI
[j] $p<0.05$ when final values of Group V were compared to final values of Group VII
[k] $p<0.05$ when initial and final values were compared in Groups II, III
[l] $p<0.05$ when initial values of Group III were compared to initial values of Groups VI, VII
[m] $p<0.05$ when final values of Groups II, IV were compared to final values of Groups II, V, VI

osmolarity and bilirubin concentration remained stable. Modified SGF resulted in lesser increases in lactic dehydrogenase, SGOT, when compared with the unmodified perfusates. Modifying the SGF plus adding methylprednisolone and allopurinol resulted in lesser increases in SGOT, lactic acid but generally did not change the perfusate concentration when compared with MSGF without additives. Use of gravity flow rather than pulsatile arterial flow resulted in marked increases in lactic dehydrogenase and lactic acid production when compared with the other perfusion techniques. Similarly, perfusion at 7C rather than 12C resulted in greater increases in lactic dehydrogenase and lactic acid production and serum ammonium levels. There were no significant changes in glucose concentration, bilirubin concentration or perfusate osmolarity during the perfusion.

Effect of Perfusion Modification on the Survival of Dogs with Auxiliary Liver Perfused for 24 Hours

Dogs receiving transplants of fresh auxiliary livers (Group I) survived a mean of 14.5 days (Table 3). When the livers were transplanted after 24 hours of hypothermic pulsatile perfusion with CPP or SGF, there was a significant reduction in survival (Table 3). Dogs transplanted with livers perfused with modified SGF, however, had significantly greater survival and the best survivals of all comparable to the transplantation with fresh liver was obtained when 24 hours of preservation with MSGF to which methylprednisolone and allopurinol had been added was utilized. Table 4 demonstrates the effect of changing perfusate temperature and/or arterial flow on the survival of dogs with auxiliary liver transplants preserved for 24 hours. Here it is apparent that substituting gravity non-pulsatile arterial flow or lowering the temperature of the perfusate to 7C had adverse effects on the survival of the dogs when compared with the use of the MSGF itself. The best results were obtained in dogs transplanted with livers perfused for 24 hours with the MSGF to which large amounts of methylprednisolone and allopurinol were added (Group VII). All dogs survived more than five days with a mean survival of 13.5 days. The causes of death are noted in Table 5.

Dogs transplanted with auxiliary liver preserved with MSGF (Group IV) and those preserved with the similar perfusate to which methylprednisolone and allopurinol were added (Group VII) had, immediately after grafting, an initial peak in the LDH and SGOT levels. Two days later these enzymes were significantly decreased. The serum bilirubin and blood ammonium were usually in the upper

TABLE 4. *Effect of Gravity Flow and 7 C Temperature on the Survival of Dogs With Auxiliary Liver Preserved for Twenty-four Hours*

	Perfusion Variables				
Groups	Perfusate	Perfusate Temperature	Perfusion Characteristics	Survivors >5 days (# dogs)	Mean Survival (Days ± SE)
IV	MSGF	10-12 C	Pulsatile arterial flow (60 mmHg) Gravity portal flow (12 cm H_2O)	4/5	11.7 ± 2.9
V	MSGF	10-12 C	Gravity arterial flow (12 cm H_2O) Gravity portal flow (12 cm H_2O)	3/5	7.2 ± 2.3
VI	MSGF	7 C	Pulsatile arterial flow (60 mmHg) Gravity portal flow (12 cm H_2O)	3/5	8.1 ± 3.4

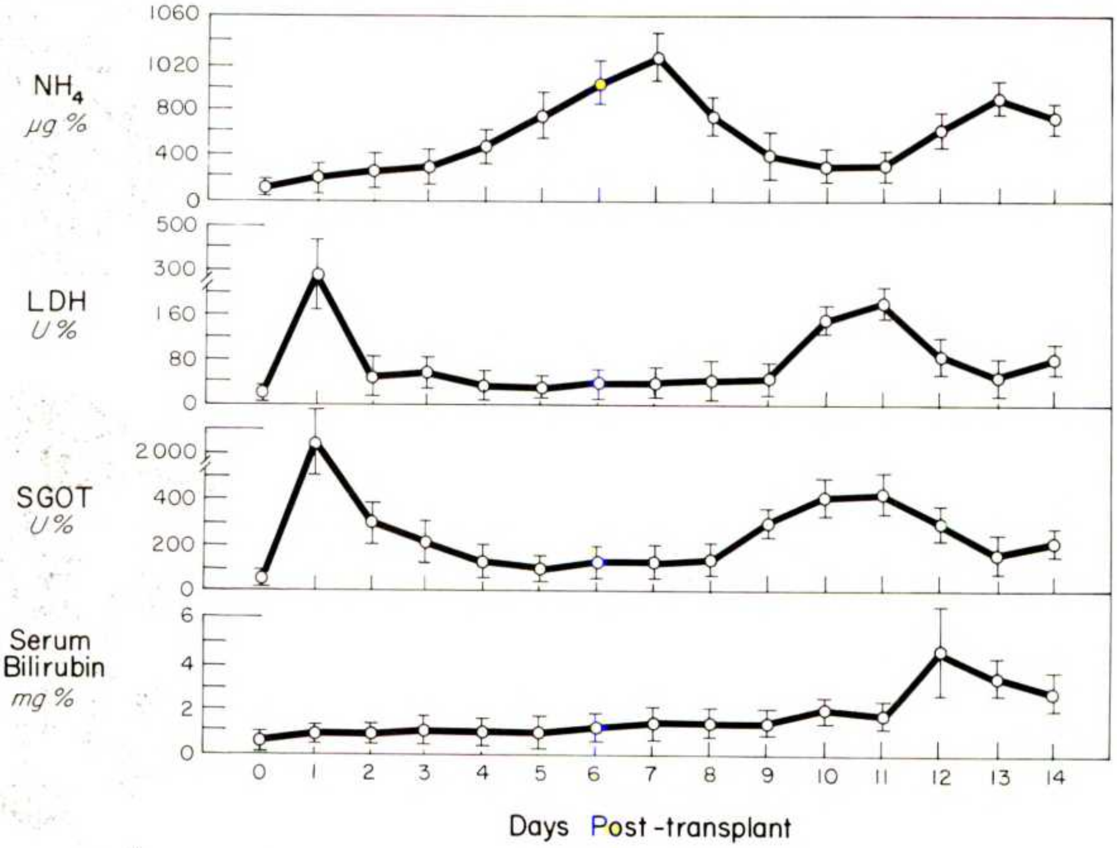


FIG. 4. Daily serum bilirubin, SGOT, LDH, and blood ammonium values (mean ± SE) in dogs transplanted with livers preserved for 24 hours with MSGF and MSGF plus allopurinol and methylprednisolone. Note an immediate rise in all values after perfusion and grafting with further decrease several days later. A second increase was observed nine days after transplantation. The blood ammonium followed a slightly different pattern.

limits in the first five days after grafting. Thereafter, the ammonium rose significantly for two days and then declined to previous levels. The SGOT and LDH began to climb eight to nine days after transplantation and decreased again two days thereafter. At the end of two weeks, all values were moderately increased (Fig. 4). Histologically there was hepatocyte preservation three weeks following transplantation with slightly central atrophy, mild bile stasis and congestion (Fig. 5).

There were no significant differences in the survival of the dogs transplanted with livers that were perfused with MSGF, pulsatile flow and 10–12C (Groups IV and VII) and the dogs transplanted with fresh liver which had no preservation (Group I). The enzymatic values (LDH, SGOT), serum bilirubin and blood ammonium posttransplantation were lower in the dogs transplanted with non-preserved livers; however, a similar pattern was observed during all post-grafting periods (Fig. 6).

Most of the dogs transplanted with livers preserved with

TABLE 5. *Cause of Recipient Death After Liver Preservation and Auxiliary Transplantation*

Cause of Death	Groups I	II	III	IV	V	VI	VII
Hepatic necrosis	1	1	0	0	1	0	0
Uncontrollable bleeding (capsular or hemorrhagic diathesis)	0	2	1	0	1	1	0
Generalized sepsis	1	1	1	0	0	1	0
Early portal vein thrombosis	0	1	1	1	1	0	0
Late portal vein thrombosis	1	0	0	1	0	1	1
Gastrointestinal bleeding	0	0	0	1	0	0	0
Small bowel necrosis	0	0	1	0	0	1	0
Celiac axis thrombosis	1	0	1	0	1	0	1
Rejection	1	0	0	1	1	0	2
Peritonitis	0	0	0	1	0	1	1

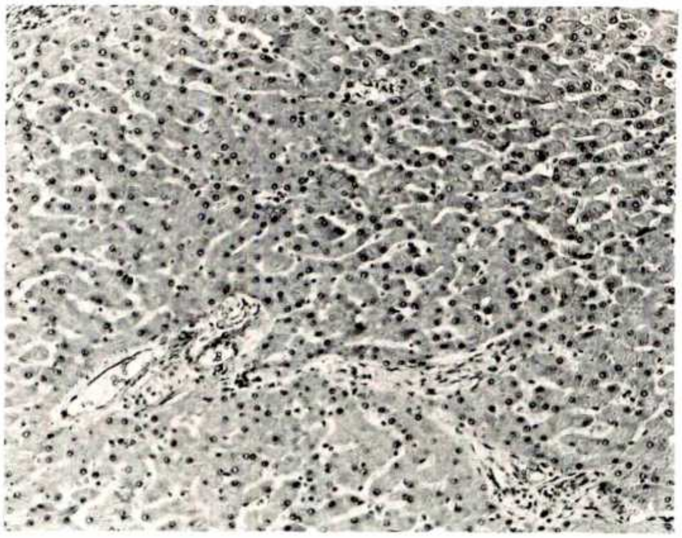


FIG. 5. Normal liver histology. Complete hepatocyte preservation after 24 hours perfusion and transplantation in one of the liver recipients of Group VII (MSGF + allopurinol and methylprednisolone) (Hematoxylin-eosin × 100).

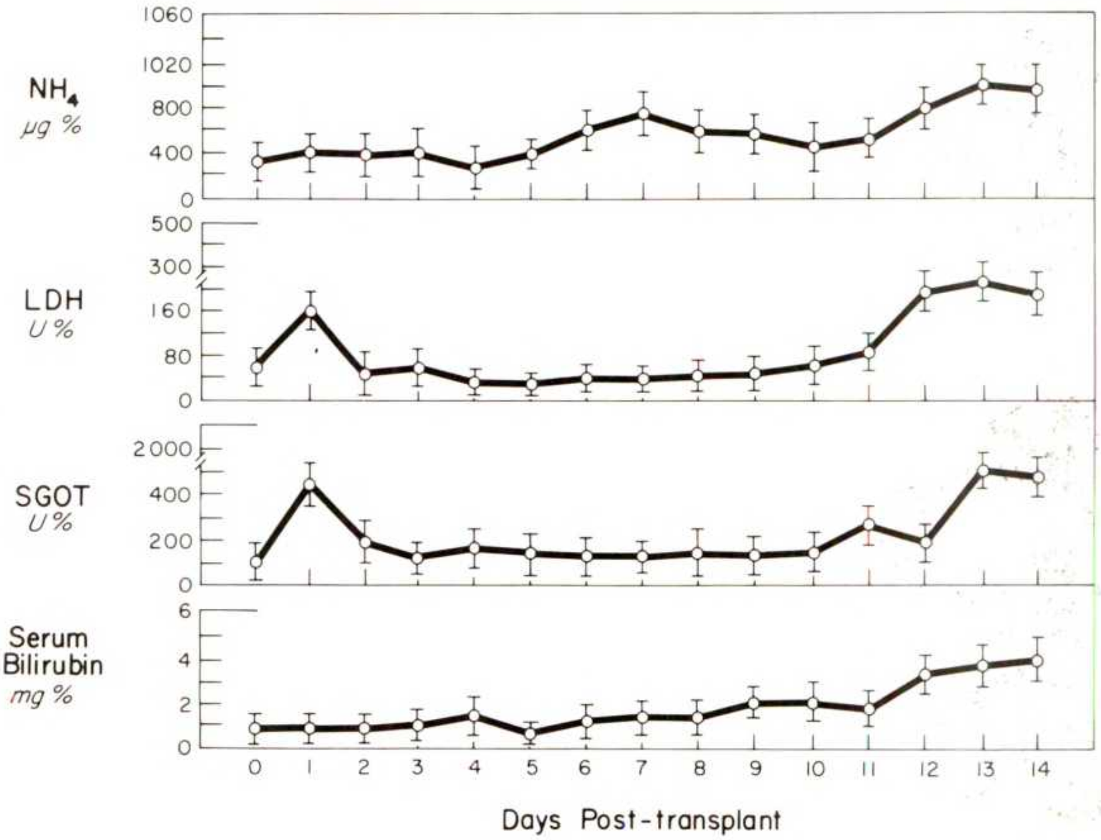


FIG. 6. Daily serum bilirubin, SGOT, LDH and blood ammonium values (mean ± SE) following transplantation of fresh livers which were not perfused prior to grafting. Note a moderate increase in all values after transplantation with further decrease two days later. A second rise was observed 11 days following transplantation. The blood ammonium followed a slightly different pattern.

CPP or SGF (Groups II, III) had a poor outcome after preservation and transplantation. These dogs had continuous rising levels of blood ammonium and serum bilirubin immediately after grafting. The LDH and SGOT ascended significantly in the first two days posttransplantation and then minimally declined to be maintained at very high levels until death (Fig. 7). Microscopically, there was massive congestion, hemorrhage, severe central atrophy and significant damage of the hepatocytes with capsular hemorrhage (Fig. 8).

Dogs transplanted with livers preserved at 7C or with gravity flow showed an initial elevation of serum LDH, SGOT, bilirubin and ammonium in the first three days after grafting. There was a decrease in the enzymatic values seven days posttransplantation with a subsequent rise three days thereafter. The serum bilirubin and blood ammonium rose again moderately before death.

Seven dogs were eliminated from the results for analysis because of technical failures which occurred during surgery and preservation. These included technical postoperative bleeding (three dogs, Groups II, III, V, one each), anesthesia complications (one dog, Group I), bronchoaspiration (one dog, Group VI), air embolii and severe acidosis during preservation (two dogs, Groups IV, VII). Four more dogs that died in the first three days after grafting were also eliminated from the study. These dogs died consecutively due to unrelated causes such as distemper (three dogs, Groups II, V, VI) and intussusception (one dog, Group III).

Discussion

Preservation of the liver offers far greater challenges than does preservation of the kidney. The present study represents a series of pilot experiments utilizing small groups of dogs to determine: 1) what flow characteristics during perfusion may be predictive of viability; 2) what chemical changes in the perfusate might be predictive of viability; 3) what modifications of perfusate composition might extend viability during perfusion; and 4) what alterations in perfusion characteristics may extend or limit viability of the perfused organ.

The basic techniques involved perfusion for 24 hours of livers which were then allotransplanted heterotopically into minimally immunosuppressed dogs with ligated portal veins. The survival of the dog was felt to depend not only on the function of the transplanted liver but also the provision, by means of the interposed transplant, for decompression of the portal circulation after portal vein ligation. If necrosis of the transplanted liver occurred due to failure to maintain viability during perfusion or rejection, the dog would die due to a combination of liver failure plus portal hypertension and intestinal congestion. It is well known that dogs do not usually survive acute portal vein ligation without portal-systemic division.[10,17,28,29] Our model of organ preservation is in no way affected by

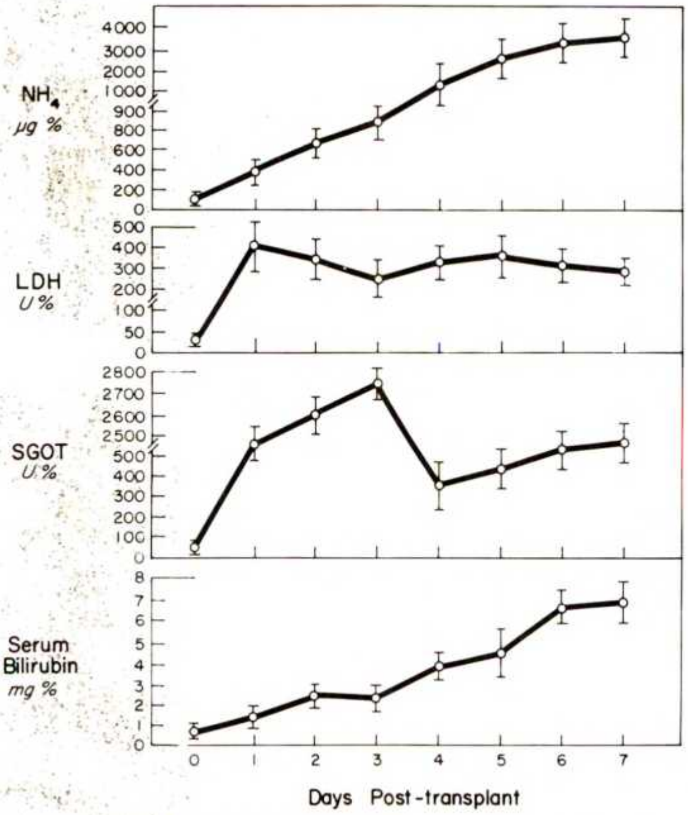


FIG. 7. Daily serum bilirubin, SGOT, LDH, and blood ammonium values (mean ± SE) in dogs transplanted with livers preserved for 24 hours with CPP and SGF. Note a continuous and significant rise in all values after preservation and transplantation. There was practically no liver function recovery after grafting.

the findings that heterotopic liver grafts atrophy with time,[14,21,34,35] or that dogs became ill after chronic portocaval diversion.[14,43,48]

Based solely on the survival of the recipient dog, it is apparent that the best perfusate consisted of MSGF, a hypertonic, hyperglycemic, hyperkalemic plasma fraction free of almost all lipoprotein, cholesterol, and fibrinogen. Only MSGF perfusion permitted recipient survival equal to the fresh transplant. Furthermore, early transplant function appeared to be as good after MSGF perfusion for 24 hours as after fresh transplantation.

MSGF was almost as good as that with methylprednisolone and allopurinol. Although one can assume that dog livers perfused with SGF or CPP are not viable enough; very few changes in the perfusate concentration during liver preservation for 24 hours hint that the MSGF or the MSGF with additives is in any way superior to CPP or SGF. Lactic dehydrogenase, SGOT, potassium and ammonium concentrations rose with all perfusates although the SGOT and lactic dehydrogenase increased less with the more successful perfusates. Measuring lactic acid, potassium and ammonium gave no assistance nor did glucose, bilirubin or osmolarity. Similarly, measuring the flow rate during the perfusion was not of great help in predicting liver viability although perfusion with MSGF with added methylprednisolone and allopurinol led to increased flow rate at 24 hours when compared with the initial flow rate. Weight gain was less with the successful MSGF perfusates and fluid loss during perfusion was minimal. Most striking was the almost double bile production when MSGF was utilized when compared with standard CPP or SGF perfusates. Thus, these findings suggest that successful perfusion with maintenance of viability of the perfused organ can be partially predicted in the failure of the lactic dehydrogenase and SGOT enzymes to increase during perfusion, failure of the flow rate to decrease and increase flow rate, a lack of weight gain, a lack of fluid loss, and marked increase in bile production. Other parameters appear less successful in predicting viability.

The mechanism by which SGF with high concentrations of potassium and glucose protected the perfused livers is not clear. It is possible that during preservation the hepatic cell membranes do not maintain stability and therefore the organ looses intracellular substances by passive diffusion. Potassium and glucose are the most important substances being extravasated during liver hypothermic preservation.[19] For this reason higher concentrations of potassium and glucose in the perfusate or extracellular space prevent a passive transport of these substances from the cells. Lie and associates[19] found that 600 mg/L of glucose and 50 mEq/L of potassium in the perfusate were the optimal concentrations for successful intermittent gravity perfusion of the porcine liver for periods up to 17 hours. The beneficial effects of SGF on perfused livers is probably related to the absence of cholesterol and fibrinogen and the relatively low values of lipoproteins in this perfusate.[37]

The addition of allopurinol to the perfusate improves *in vitro* function and posttransplant survival probably by pro-

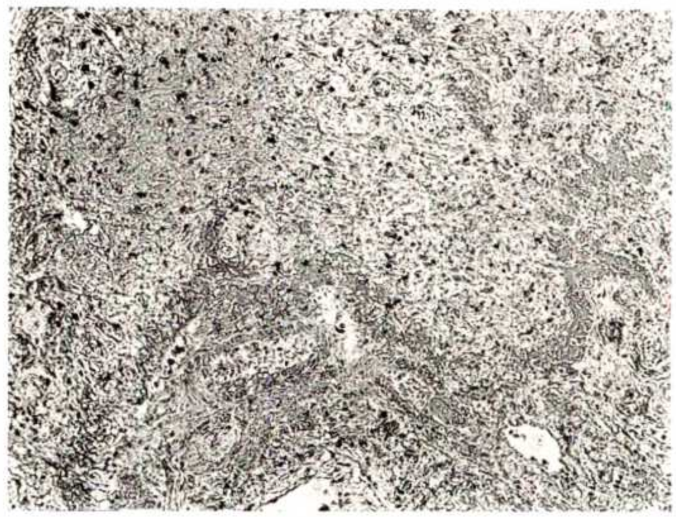


FIG. 8. There is massive congestion, hemorrhage, severe central atrophy and significant hepatocyte damage in one of the liver recipients transplanted after perfusion with CPP (Hematoxylin-eosin × 40).

ducing vasodilation and increasing the nucleotide pool with consequent conservation of energy.[38] Birbaum and colleagues[4] observed that the addition of high-energy electron bonds such as ATP, NAD, and FAD in the perfusate did not maintain the viability of transplanted dogs with liver perfused for 24 hours. Some of the signs of cellular damage during perfusion, such as potassium leak and low glucose and oxygen utilization, were reversed by the addition of ATP to the liver perfusion system.

The use of allopurinol combined with high doses of methylprednisolone (2.0 gm/L) determined a better outcome of the perfused and transplanted livers. The beneficial effect of methylprednisolone in the perfused organs is based on its action of stabilizing membrane lysosomes and improving tissue perfusion. However, regular doses of methylprednisolone (800 mg/L) routinely used in kidney preservation did not demonstrate any beneficial effect on livers perfused for 24 hours.

Belzer and his group[2] found the endothelial integrity of the sinusoids consistently damaged after 10 hours of pulsatile perfusion with cryoprecipitated plasma.[2] All porcine livers perfused for 24 hours died immediately after transplantation. Brettschneider and associates[5] perfused successfully canine livers under hypothermic perfusion and hyperbaria from eight to 25 hours. The animals transplanted with poor perfused livers died within three days after grafting with severe ischemic injury and clotting abnormalities. These problems have frequently been reported by other investigators.[8,9,11–13,15,16,20,22,30,32,33] Calne and his group,[6] with a single passage of intermittent squint perfusion through the pig's liver, were able to obtain long-term survivors after liver preservation for 12-17 hours.

Elmslie and associates[11] demonstrated that perfusion of the pig liver at 13-15C for several hours did not cause any deterioration in the ability of the rewarmed liver to excrete bromosulphalein. On the contrary, liver temperatures of 13-22C appeared to enhance the ability to excrete bromosulphalein. Castillo-Olivares and colleagues[7] found a protection of the mitochondrial respiration and the oxidative phosphorylation during hepatic preservation at 4C for three hours. Similar studies at 22C resulted in a severe impairment of the liver mitochondrial functions one hour after the beginning of preservation. The mechanism by which cold preservation protects mitochondrial respiration is based in the easy denaturation of mitochondrial enzymes due to temperature.[7] However, 4C cooling did not prevent the mitochondria from becoming uncoupled after three hours of liver preservation. It is probably that after this time cold anoxia is the main factor in determining mitochondrial deterioration. In our system, although the best results were observed in the dogs transplanted with livers perfused at 10-12C for 24 hours, there were not significant differences (p 0.08) in survival of dogs with transplanted livers that were perfused at 7C. Equally good results were obtained in livers perfused under pulsatile perfusion for 24 hours. Dogs transplanted with livers perfused with only gravity flow for the same period of time has a lower survival time with similar flow rates.

Marchioro and associates[21] reported on the competition for nutritional substrates that occurs in the presence of two livers. They concluded that the allografted organ must receive its portal supply from the intestinal venous return. We observed similar results on livers perfused for 24 hours and then transplanted with splanchnic flow diverted to the auxiliary graft. However, van der Heyde and colleagues[9,46] have shown that liver grafts deprived of portal inflow do not necessarily atrophy if the host liver is subjected to a physiological disadvantage. These results have been confirmed by Uchida and colleagues[45] and Bengochea-Gonzalez and associates.[3] Wexler and his group[48] recently performed 70% hepatectomy and bile duct ligation of dogs that had auxiliary liver transplantation without portal vein anastomosis. Their results indicated that atrophy of the grafted liver was consistently present only if the renal vein to portal vein anastomosis was thrombosed; otherwise, the grafted organs maintained similar pre-operative weights.

Twenty-four hours of liver preservation caused severe hepatic damage in the absence of a modified silica gel fraction which had high levels of potassium and glucose during perfusion. The addition of allopurinol and high doses of methylprednisolone to the perfusate allowed a complete protection of the perfused livers and all the transplanted dogs survived for long periods of time. The use of nonpulsatile flow or temperature of 7C during perfusion did not efficiently protect the liver perfused for 24 hours. Only pulsatile flow through the celiac axis and gravity flow through the portal vein with a temperature of 10-12C determined long-term survivors of all recipient dogs.

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Treatment of Intra-abdominal and Abdominal Wall Desmoid Tumors With Drugs That Affect the Metabolism of Cyclic 3', 5'–Adenosine Monophosphate

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A female patient with Gardner's syndrome was treated with Δ¹-testololactone (200 mg daily) because of growth of a large desmoid tumor in the pelvis and lower abdomen and a tumor in a scar from a previous laparotomy. There was also pain and swelling of the left leg. An immediate effect of the drug therapy was complete relief of pain followed shortly thereafter by disappearance of the edema of the leg. After two months, the numerous sebaceous cysts were less prominent. The gross measurements of the diameter of the pelvic and lower abdominal tumor clearly demonstrated tumor shrinkage following therapy. Small polyps scattered over the rectal mucosa and numerous osteomata were not demonstrably affected. After one year of treatment with Δ¹-testololactone, a laparotomy for partial small bowel obstruction was necessary. Obstruction was caused by the involvement of small bowel mesentery and the bowel itself in a contracted residuum of dense fibrous tissue. Substitution of theophylline and chlorothiazide for the testololactone in January 1974 was followed by further diminution of the measurable abdominal and pelvic desmoids. All of these compounds synergize the action of 3', 5'—adenosine monophosphate and at least the latter two may function by inhibiting the action of 3', 5'—adenosine monophosphate diesterase.

THE TREATMENT of patients with Gardner's syndrome is unsatisfactory in many respects. Polyposis of the colon has usually been considered sufficient indication for subtotal or total colectomy to prevent development of carcinoma. On the other hand, polyps of the duodenum usually have been kept under observation or excised locally, and polyps of the small intestine have been similarly managed except when malignancy developed. Various palliative operations have been carried out for desmoid tumors in the abdominal cavity, retroperitoneal area or abdominal wall but these lesions are often inoperable, amenable to only partial excision or capable of removal only with great risk of complication and mortality.[13–15,23,25] Furthermore, local recurrence is common and outright fibrosarcoma development from tumors whose early growth patterns and histologic characteristics have appeared benign has been reported.[5,8–10,17,23,25,33,36–38,44,45,47,50] The biologic problems of desmoid tumor control are related to such non-neoplastic lesions as retroperitoneal fibrosis,[25] juvenile fibromatosis,[26] congenital generalized fibromatosis[4,43] and other poorly characterized pathologic conditions.[3,26,12]

This report concerns the chemical treatment of intra-abdominal and abdominal wall desmoid tumors with Δ¹-testololactone for one year and then attainment of further improvement over a six-month period when the patient was taking theophylline (Choledyl (R_x)) and chlorothiazide (Diuril (R_x)). These compounds are inhibitors of cyclic adenosine monophosphate (cAMP) phosphodiesterase (PDE). There is an extensive literature concerning the *in vitro* effects of cAMP on tumor cells.[7,16,20–22,24,30,39,40,42,51] Growth of tumors can also be inhibited *in vivo*.[11]

Case Report

C.G.H. No. 382891. A 23-year-old woman entered Colorado General Hospital April 11, 1971 with a diagnosis of familial Gardner's syndrome. She was known to have had colon polyps for nine years since the time of the first examination of the colon. Admission was prompted by radiographically demonstrated rapid growth of polyps in the transverse colon. Other stigmata of Gardner's syndrome included a presumed desmoid tumor underlying and involving an old appendectomy scar in the right

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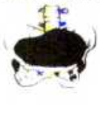
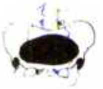
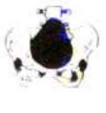
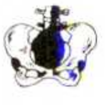
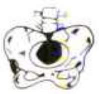
Date	Transverse cm	Vertical cm	Protrusion beyond anterior iliac spine	Silhouette to approximate scale
Jan. 1973	15.0	7.0		
March 1973	12.0	7.0	4.5	
June 1973	9.5	6.5	4.0	
Sept. 1973	9.0	10.5	3.5	
Jan. 1974	7.5	14.0	1.5	
June 1974	6.5	6.5	1.0	

TABLE 1. Measurements of pelvic tumor. These measurements are approximate and represent the presentation of the tumor anteriorly. As the intra-abdominal tumor mass decreased in size, the abdominal wall mass became evident. This is believed to account for the changed general shape of the tumor and the apparent increase in the vertical dimension after six months. See case report for details. No sketch of the tumor was made in June 1973. Δ^1-testololactone was administered in 1973, chlorothiazide and theophylline thereafter.

lower quadrant, multiple sebaceous cysts and osteomata in the ribs, mandibles, calvarium and pelvis. Several subcutaneous desmoid tumors had previously been removed from the abdominal wall. There was a history of frequent migraine headaches and of duodenal ulcer demonstrated radiographically. The patient's mother, maternal grandmother, two uncles and an aunt had Gardner's syndrome. Only one uncle still survived at this time, the affected relatives having died of desmoid tumors and/or complication of the primary disease. Numerous laboratory tests on the patient were all normal except for the results of radiologic examination of bones and colon. On April 14, 1971 subtotal colectomy, splenectomy and partial resection of the diaphragm were carried out. The latter organs were removed because of the presence of a fibrotic mass overlying the upper pole of the spleen and involving the diaphragm. It was initially thought to be a malignancy. Bilateral tubal ligation was performed. The polyps in the colon were benign and the mass involving the spleen and diaphragm was made up of acellular fibrous tissue. The patient's convalescence was complicated by left lower lobe streptococcal pneumonia and serous pleural effusion. The response to antibiotics was satisfactory and the patient experienced uneventful convalescence from that time on.

In January 1973 the patient was hospitalized again for removal of enlarging abdominal wall and pelvic desmoids. For several months she had had pain radiating down the left thigh posteriorly and medially. In addition, the left leg and foot became swollen when she remained upright to carry on her work as a beautician. There was a hard, fixed mass (15 × 7 cm) involving the lower abdominal wall and bony pelvis which was considered inoperable because of its size and fixation to surrounding structures. Previous descriptions of the desmoid tumor were meager with no recorded measurements. Osteomas in the mandibles, ribs and pelvic bones were again noted. A 2 × 3 cm firm tumor mass had grown in the center of the laparotomy scar. A few mucosal polyps in the remaining rectum were noted. Because the desmoid tumor in the lower abdomen and pelvis was symptomatic and considered inoperable, the patient was started on Δ^1-testololactone (Teslac [R_x]) in a dose of 50 mg four times daily by mouth. The patient provided a clue for this approach when she related that the numerous sebaceous cysts over her body, particularly on her scalp and face, had enlarged when she was taking birth control pills and receiving injections of provera for six months in 1969 and 1970. They regressed somewhat when this medication was stopped.

The patient was re-evaluated in March 1973. She had no further pain in the left thigh. Whereas she had been previously taking Darvon daily, she had taken only two tablets after hospitalization in January. There was no swelling of the foot and leg even though she customarily worked 12 hours a day. The tumor in the laparotomy incision had gradually disappeared, leaving only a thickened area. The transverse diameter of the abdominal and pelvic desmoid, previously 15 cm, was recorded as 12.0 and 13.5 cm by two different observers (Table 1). The vertical measurement in the midline was found to be 7.0 and 7.5 (previously 7.0). Twelve mucosal polyps in the rectum were fulgurated. The patient was discharged back to her home in Wyoming with instruction to continue the Δ^1-testololactone, 200 mg daily.

The patient was re-evaluated in June 1973. The desmoid was irregularly contracted. The transverse diameter was 9.5 cm and the vertical diameter was 6.5 cm. In contrast to the previous fixed status, the mass was now movable in all directions. About one month previously there had been a 24-hour episode of pain and tenderness in the tumor after which it became softer. Frequent nausea, occasional vomiting and increased frequency of loose stools occurred, possibly as side effects of the Δ^1-testololactone. There was a definite increase in acne but the sebaceous cysts and osteomas appeared unchanged. Extensive laboratory measurements including 17 hydroxysteroids, 11 oxysteroids, aldosterone and blood cortisol were all normal. Three minute polyps were visualized in the remaining rectal mucosa.

There were short hospitalizations in September 1973 and January 1974 for the purpose of evaluating the status of the tumor, rectal polyps, osteomas and sebaceous cysts. The large desmoid was smaller as shown in Table 1. The tumor in the wound had completely disappeared. There were 13 tiny polyps in the rectal mucosa in September 1973; five were found in January 1974 and four in June 1974. The osteomas had not changed. Acne on the face had healed remarkably. The numerous sebaceous cysts were the same except that three lesions had ruptured spontaneously several months previously and had not reformed. At the January 1974 admission the patient complained of attacks of abdominal pain and diarrhea. Radiologic examination of the gastrointestinal tract showed a partially obstructed and grossly dilated loop of mid-jejunum. On January 18 1974 a laparotomy was carried out to relieve this lesion. The observations during the operation were somewhat at a variance from the interpretations and measurements made from physical examination. In the first place, there were numerous patches of desmoid tumor formation throughout the abdomen, particularly in the large bowel mesentery. The measurements shown in Table 1 for January 1973 were probably of a pelvic desmoid tumor which had contracted to a small irregular mass no more than 2–3 cm in diameter in the mesentery of the terminal ileum. The bowel was adherent to and caught in this contracted remnant with conformation like the bows of a Christmas package ribbon.

The tumor measurements of September 1973, January 1974 and June 1974 were of a flattened mass of desmoid tumor in the abdominal wall and extending out from the incision to the extent indicated by the measurements. It could have been resected in January, but there would have been a large abdominal wall defect and the decision was made to rely on chemical control of this tumor along with the numerous other intra-abdominal tumors. Δ^1-testololactone was discontinued because of menorrhagia and concomitant anemia. Theophylline (Choledyl (R_x), 400 mg daily) and hlorothiazide (Diuril (R_r). 500 mg daily) were substituted for Δ¹-stololactone. This desmoid tumor continued to shrink as shown in Table . Acne cleared completely. The osteomata and sebaceous cysts remained nchanged.

Discussion

Biopsies taken from normal and tumorous regions in this atient have been used to establish tissue cultures in which esponse to various drug administrations is under study. he fortuitous recognition of a significant feature in a emale Gardner's syndrome patient's history involving the dverse effects of birth control medication has led to what ppears to be a method of control of her desmoid tumors. he patient noted the growth of sebaceous cysts while on hese drugs. Long after this episode and presumably stimuated by laparotomy and subtotal colectomy, previous uiescent desmoid tumors in the pelvis enlarged over the ourse of about one year to a point where they were consilered inoperable or at the very least requiring very extenive operation. The probability of growth of new tumors ollowing operation also served to contraindicate further urgery since a hard tumor mass was noted in the most ecent laparotomy incision. The situation was charged with motional apprehension stemming from long and fatal llnesses of the patient's mother and a maternal uncle from lesmoid tumors. The former died of inanition after multiple mall bowel resections necessitated by necrosis of the owel as a retroperitoneal desmoid occluded arterial blood upply to the intestine. The uncle died of respiratory failure nd pulmonary infection secondary to encroachment of an normous desmoid tumor in the upper abdomen. The paient and her husband, as well as their doctors, were willing o pursue any alternative therapeutic lead, however slight ts chance of success.

A second consideration was a scattered and long history f laboratory and experimental investigations of the etiolgy of desmoid tumors indicating some endocrine abnornality and trauma as the outstanding etiologic features.[6,23,27–29,32,34–36] Administration of testosterone has een recorded in two cases without success (Reference 4 in Iunt *et al.*, 23 and 5). It has been shown that a high percenage of the cases with desmoid tumor occur in adult females nd that the growth of tumors is sometimes stimulated by regnancy and parturition, although the condition can ccur in males, in children and usually without a demontrable familial incidence. Assays of estrogen and onadotropins have been carried out, but the results have een inconclusive, perhaps because of the relatively rimitive methods of assay available at that time.[36] xperimental production of fibrous tumors of the abdomnal organs, the anterior abdominal wall and thorax in uinea pigs with estrogen preparations has been studied n detail by Lipschütz and co-workers[6,27–29] and thers.[32,34,35] In one study, inhibition of development of uch tumors by progesterone and some closely related compounds that interfere with the effect of estrogens was reported.[28] Other rodents, however, were not susceptible.

The selection of a drug for trial in this case was an extension of laboratory and clinical trials of Δ¹-testololactone in conjunction with 5-fluorouracil for advanced malignancy. The combination of Δ¹-testololactone and 5-fluorouracil proved partially effective in carcinoma of the pancreas,[48] and the combination is known to induce remission in about 50% of patients with disseminated carcinoma of the breast.[19] Δ¹-testololactone by itself causes remission in 10–20% of patients with breast carcinoma.[18,41] Especially attractive features of this drug are lack of toxicity and absence of endocrine effects. The mechanism by which this drug affects cancer of the breast and how it potentiates the effect of 5-fluorouracil in carcinoma of the pancreas are not known. Various enzymes are affected[1] and the suggestion has been made that interference with normal steroid metabolism by microsomal enzymes of the smooth endoplasmic reticulum occurs.[48] Synergism with estrogen in inhibiting tumor growth of a transplantable lactating mammary adenocarcinoma in Fischer rats has been reported.[1] It is of some interest that one of the possibilities examined by Lipschütz and Grismali[28] many years ago in a study of natural and synthetic steroid inhibitors of estrogen-induced fibroma was that unsaturation in the A ring of steroids was a requisite for inhibition. These investigators were also impressed by the presence of substitution on the 17 carbon which would, of course, not be fulfilled by Δ¹-testololactone although the similarity to progesterone is otherwise close.

More recent experiments have shown striking effects of dibutyryl 3′,5′-cyclic adenosine monophosphate and testosterone in promoting differentiation of transformed cultured Chinese hamster ovarian cells to mature fibroblasts. In addition, Δ¹-testololactone was tested with dibutyryl 3′,5′-cyclic AMP and found to be even more effective than testosterone.[21,22,39,40] The chemical mechanism of this effect on differentiation has not been further elucidated but a phenomenon of fundamental importance seems to have been uncovered. In parallel studies, reverse transformation of cultured sarcoma cells on exposure to 3′,5′-cyclic AMP was shown by Johnson, Friedman and Pastan.[24]

Recently, data have appeared concerning the effect of a wide variety of drugs of different classes on cAMP phosphodiesterase activity of rat brain and cat heart.[52] This survey revealed two facts believed important to understanding of the effect of Δ¹-testololactone on certain cells in which "reverse transformation" can be demonstrated.[39] In the first place, Δ¹-testololactone by itself has some inhibitory effect on cAMP phosphodiesterase. Even more important is the finding that estradiol is a potent inhibitor of this enzyme. This seems particularly pertinent in view of observations from this laboratory showing that in mouse hepatoma Δ¹-testololactone impairs metabolism of estradiol and causes accumulation of this administered compound in tumor cells.[2]

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Maalox is a colloidal suspension of magnesium and aluminum hydroxides useful for the relief of gastric hyperacidity and heartburn.
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Available in two dosage strengths:
No. 2 — ¼ grain (16.2 mg.)
Codeine Phosphate
No. 3 — ½ grain (32.4 mg.)
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... both with five grains of Maalox-protected aspirin.

Ascriptin,® an excellent analgesic, antipyretic, and anti-inflammatory, combined with codeine to give effective relief from severe pain with minimal aspirin-induced gastric distress.

Indication: As an analgesic for the relief of pain of all degrees of severity up to that which requires morphine.

Side Effects: Side effects are rare. Nausea, constipation and drowsiness may occur.

Warning — may be habit forming.

Usual Adult Dose: Ascriptin with Codeine No. 2 (¼ grain): Two tablets every 3 or 4 hrs. when necessary.

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the low-back patient and his problems:

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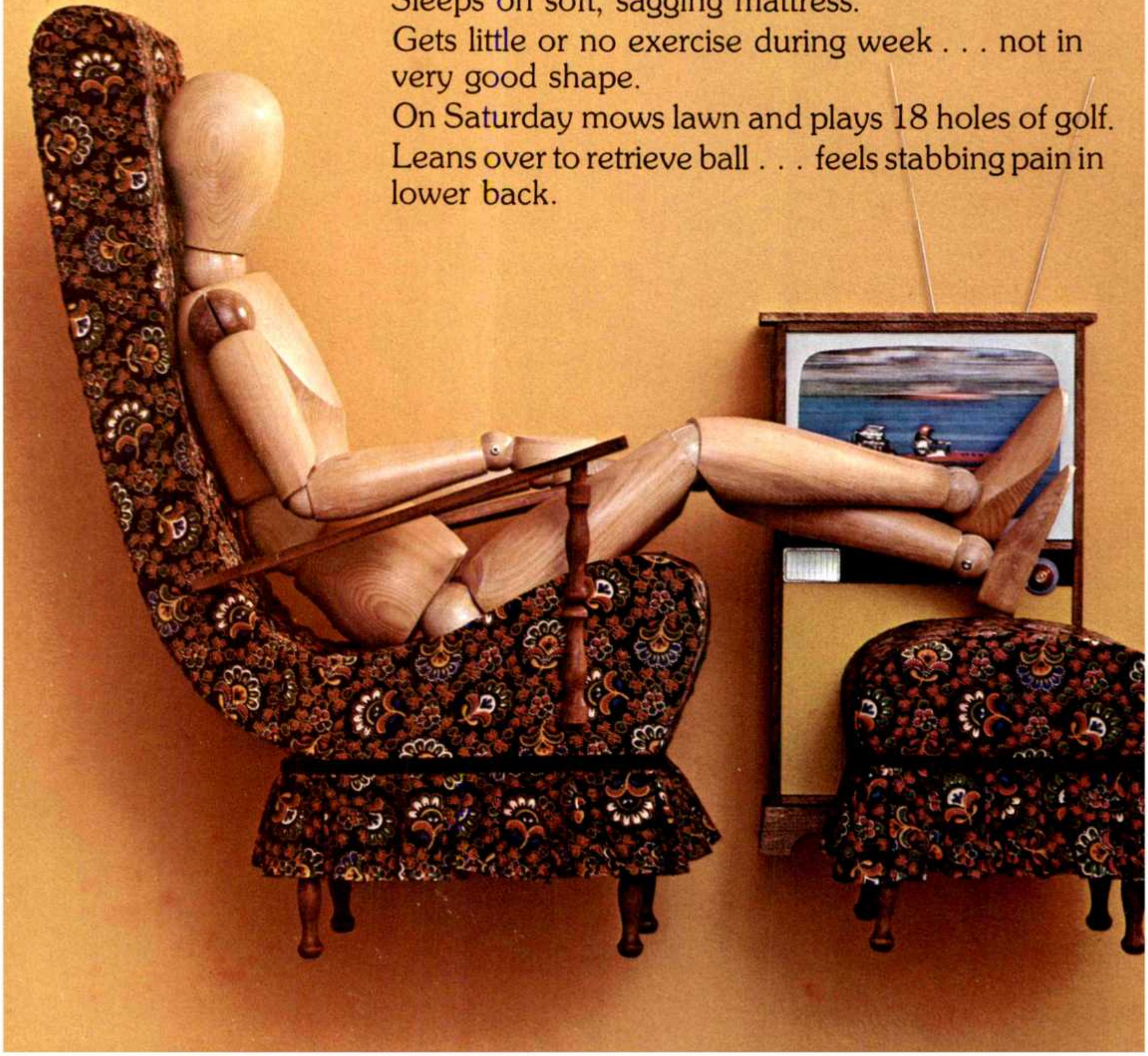
Sedentary job. Sits most of day in plush swivel chair.
Sits slumped in overstuffed furniture at home.
Sleeps on soft, sagging mattress.
Gets little or no exercise during week . . . not in very good shape.
On Saturday mows lawn and plays 18 holes of golf.
Leans over to retrieve ball . . . feels stabbing pain in lower back.



the solution:

At work sit in straight chair with firm back . . . knees higher than hips. Prop feet on small footstool to elevate knees. Don't sit in overstuffed furniture. Never sit long in one position . . . get up frequently and move around. Exercise regularly to strengthen abdominal and low-back muscles and help prevent weekend flare-ups. Avoid sudden spurts of vigorous physical activity. A back support can help relieve pain and fatigue.

to relieve discomforts associated with acute, painful musculoskeletal disorders...

ROBAXIN®-750

brand of

methocarbamol 750 mg. capsule-shaped tablets

the Robaxin Regimen:

Complete bed rest on a very firm mattress is usually indicated in the home treatment of acute low-back discomfort. Have patient insert section of plywood ½-¾" thick between mattress and box springs. The use of moist heat is often very beneficial.

Robaxin-750 is often indicated to relieve the discomforts associated with acute, painful musculoskeletal disorders. It is a well tolerated agent which can provide significant relief, usually without serious adverse reactions.

Indications:
As an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions. The mode of action of this drug has not been clearly identified, but may be related to its sedative properties. Methocarbamol does not directly relax tense skeletal muscles in man.

Contraindications:
Robaxin is contraindicated in patients hypersensitive to any of the ingredients.

Warnings:
Safe use of Robaxin has not been established with regard to possible adverse effects upon fetal development. Therefore, Robaxin should not be used in women who are or may become pregnant and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the possible hazards.

Precautions:
Safety and effectiveness in children below the age of 12 years have not been established.

It is not known whether this drug is secreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Methocarbamol may cause a color interference in certain screening tests for 5-hydroxyindoleacetic acid (5-HIAA) and vanilmandelic acid (VMA).

Adverse Reactions:
Lightheadedness, dizziness, drowsiness, nausea, allergic manifestations such as urticaria, pruritus, rash, conjunctivitis with nasal congestion, blurred vision, headache, fever.

Dosage and Administration:
Initial dosage, 2 tablets q.i.d.; maintenance dosage, 1 tablet q.4h. or 2 tablets t.i.d.

Six grams a day are recommended for the first 48 to 72 hours of treatment. (For severe conditions 8 grams a day may be administered.) Thereafter, the dosage can usually be reduced to approximately 4 grams a day.

Also Available:
ROBAXIN® (methocarbamol) 500 mg.

See package insert for full prescribing information.

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Effective performance in postsurgical and other serious susceptible hospital infections

Bacteriologically controlled studies demonstrated efficacy in patients with:

- Skin and soft-tissue infections due to *Staphylococcus aureus*, including penicillin G-resistant staph, Group A beta-hemolytic streptococci or *E. coli.*
- Respiratory tract infections due to *D. pneumoniae*, Group A beta-hemolytic streptococci, Klebsiella spp. or *H. influenzae.*
- Genitourinary tract infections due to *E. coli*, *P. mirabilis*, Klebsiella spp. or *Staphylococcus aureus*, including penicillin G-resistant staph

Low incidence of venous irritation on I.V. administration... well tolerated locally

In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low. *Controlled studies* in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly.

Cephalosporins are reported to produce maculopapular rash, urticaria, reactions resembling serum-sickness and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

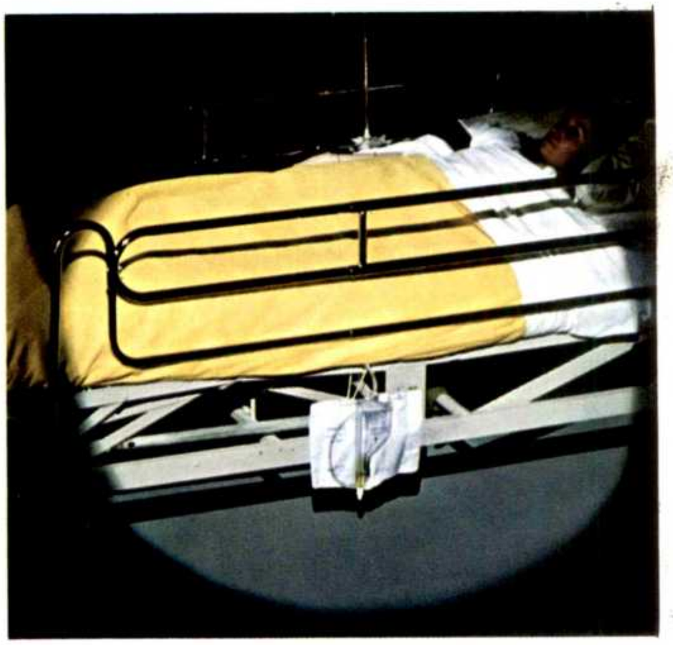
In penicillin-allergic patients, cephalosporins should be used with great caution. There is clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins, and there are instances of patients who have had reactions to both drugs (including fatal anaphylaxis after parenteral use).

Flexible Dosage: adjustable to fit severity of infection and renal status of patient:

The usual adult dose of Cefadyl is 0.5 Gm. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. Doses up to 12 Gm. daily may be used in very serious or life-threatening infections.

No nephrotoxicity reported during extensive clinical trials

In fact, when Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported. However, renal status of patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate. Rises in BUN have been observed; their frequency increases in patients over 50 years old. (See Dosage, Adults—in Prescribing Information on last page.)



New

Cefadyl® IV/IM

sterile
cephapirin sodium

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BRISTOL

Cefadyl® IV/IM

sterile
cephapirin sodium

Effective performance in surgical and other serious susceptible hospital infections

CEFADYL® (sterile cephapirin sodium) 7628 DIRO-07 July 1974

Description. Cefadyl (sterile cephapirin sodium) is a cephalosporin antibiotic intended for intramuscular and intravenous administration only. It is supplied as the sodium salt of 7-[α-(4-pyridylthio)-acetamido]-cephalosporanic acid. Each 500 mg. contains 1.18 milliequivalents of sodium.

Actions. *Human Pharmacology*—Following intramuscular administration of single 500-mg. and 1-Gm. doses to normal volunteers, average peak serum levels of 9.0 and 16.4 mcg./ml. respectively, were attained at 30 minutes, declining to 0.7 and 1.0 mcg./ml. respectively, at 4 hours and 0.2 and 0.3 mcg./ml. respectively, at 6 hours.

Cefadyl and its metabolites were excreted primarily by the kidneys. Antibiotic activity in the urine was equivalent to 35% of a 500-mg. dose 6 hours after I.M. injection, and to 65% of a 500-mg. dose 12 hours after injection. Following an I.M. dose of 500 mg., peak urine levels averaged 900 mcg./ml. within the first 6 hours.

Following rapid intravenous administration of single 0.5-Gm., 1-Gm., and 2-Gm. doses, peak serum levels of 35, 67, and 129 mcg./ml. respectively, were attained at 5 minutes, declining to 6.7, 14.0, and 31.7 mcg./ml. respectively, at 30 minutes and 0.27, 0.61, and 1.11 mcg./ml. respectively, at 3 hours.

Seventy percent of the administered dose was recovered in the urine within 6 hours. Repetitive intravenous administration of 1-Gm. doses over 6-hour periods produced serum levels between 4.5 and 5.5 mcg./ml.

44 to 50% of Cefadyl is bound to human serum. The average serum half-life of Cefadyl in patients with normal renal function is approximately 36 minutes.

The major metabolite of cephapirin is desacetyl cephapirin which has been shown to contribute to antibacterial activity.

Controlled studies in normal adult volunteers revealed that Cefadyl was well tolerated intramuscularly. In controlled studies of volunteers and of patients receiving I.V. Cefadyl, the incidence of venous irritation was low.

Microbiology—*In vitro* tests demonstrate that the action of cephalosporins results from inhibition of cell-wall synthesis. Cefadyl is active against the following organisms *in vitro:*

Beta-hemolytic streptococci and other streptococci. (Many strains of enterococci, e.g., *S. faecalis*, are relatively resistant.)

Staphylococci, including coagulase-positive, coagulase-negative, penicillinase, and non-penicillinase producing strains. *Diplococcus pneumoniae, Haemophilus influenzae, Proteus mirabilis, Escherichia coli,* Klebsiella species.

Most strains of enterobacter and indole-positive Proteus (*P. vulgaris, P. morganii, P. rettgeri*) are resistant to Cefadyl. Methicillin-resistant staphylococci, Serratia, Pseudomonas, Mima, and Herellea species are almost uniformly resistant to Cefadyl.

Disc Susceptibility Tests—Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. One such procedure* has been recommended for use with discs for testing susceptibility to cephalosporin class antibiotics. Interpretations correlate diameters of the disc test with MIC values for Cefadyl. With this procedure, a report from the laboratory of "susceptible" indicates that the infecting organism is likely to respond to therapy. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used, or if the infection is confined to tissues and fluids (e.g., urine), in which high antibiotic levels are attained.

Indications. Cefadyl is indicated in the treatment of infections caused by susceptible strains of the following microorganisms:

Group A beta-hemolytic streptococci: Skin and soft tissue infections. Respiratory infections.

(Injectable benzathine penicillin is considered to be the drug of choice in treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Cefadyl is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Cefadyl in the subsequent prevention of rheumatic fever are not available at present.)

Staphylococcus aureus (penicillinase producing and non-penicillinase producing): Skin and soft tissue infections. Urinary tract infections.

Diplococcus pneumoniae: Respiratory tract infections.

Haemophilus influenzae: Respiratory tract infections.

Escherichia coli: Urinary tract infections, skin and soft tissue infections, and bacteremia.

Klebsiella species: Urinary tract and respiratory tract infections.

Proteus mirabilis: Urinary tract infections.

Note: Appropriate bacteriological studies should be performed to identify the causative organism and determine its susceptibility. Therapy may be started while awaiting results of these studies.

Contraindications. Cefadyl (sterile cephapirin sodium) is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings. IN PENICILLIN-ALLERGIC PATIENTS, CEPHALOSPORINS SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary. No exceptions should be made with regard to Cefadyl.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE. OXYGEN, INTRAVENOUS STEROIDS, ANY AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions. The renal status of the patients should be determined prior to and during Cefadyl therapy, since in patients with impaired renal function, a reduced dose may be appropriate (see *Dosage, Adults*). When Cefadyl was given to patients with marked reduction in renal function and to renal transplant patients, no adverse effects were reported.

Prolonged use of Cefadyl may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

With high urine concentrations of cephapirin, false-positive glucose reactions may occur if Clinitest, Benedict's Solution, or Fehling's Solution are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix or Tes-Tape) be used.

Adverse Reactions. *Hypersensitivity*—Cephalosporins were reported to produce the following reactions: maculopapular rash, urticaria, reactions resembling serum sickness, and anaphylaxis. Eosinophilia and drug fever have been observed to be associated with other allergic reactions. These reactions are most likely to occur in patients with a history of allergy, particularly to penicillin.

Blood—During large scale clinical trials, rare instances of neutropenia, leukopenia, anemia were reported. Some individuals, particularly those with azotemia, have developed positive direct Coombs test during therapy with other cephalosporins.

Liver—Elevations in SGPT or SGOT, alkaline phosphatase, and bilirubin have been reported.

Kidney—Rises in BUN have been observed; their frequency increases in patients over 50 years old.

Dosage. *Adults*—The usual dose is 500 mg. to 1 Gm. every 4 to 6 hours intramuscularly or intravenously. The lower dose of 500 mg. is adequate for certain infections, such as skin and soft tissue and most urinary tract infections. However, the higher dose is recommended for more serious infections.

Very serious or life-threatening infections may require doses up to 12 Grams daily. The intravenous route is preferable when high doses are indicated.

Depending upon the causative organism and the severity of infection, patients with reduced renal function (moderately severe oliguria or serum creatinine above 5.0 mg./100 ml.) may be treated adequately with a lower dose, 7.5 to 15 mg./Kg. of cephapirin every 12 hours. Patients with severely reduced renal function and who are to be dialyzed should receive the same dose just prior to dialysis and every 12 hours thereafter.

Children—The dosage is in accordance with age, weight, and severity of infection. The recommended total daily dose is 40 to 80 mg./Kg. (20 to 40 mg./lb.) administered in four equally divided doses.

The drug has not been extensively studied in infants; therefore, in the treatment of children under the age of three months the relative benefit/risk should be considered.

Therapy in beta-hemolytic streptococcal infections should continue for at least 10 days.

Where indicated, surgical procedures should be performed in conjunction with antibiotic therapy.

Administration. Cefadyl may be administered by the intramuscular or the intravenous routes.

Intramuscular Injection—The 1-Gm. vial should be reconstituted with 2 ml. of Sterile Water for Injection, U.S.P. Each 1.2 ml. contains 500 mg. of cephapirin. All injections should be deep in the muscle mass.

Intravenous Injection—The intravenous route may be preferable for patients with bacteremia, septicemia, or other severe or life-threatening infections who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending. If patient has impaired renal function, a reduced dose may be indicated (see *Dosage, Adults*). In conditions such as septicemia, 6 to 8 Gm. per day may be given intravenously for several days at the beginning of therapy; then, depending on the clinical response and laboratory findings, the dosage may gradually be reduced.

When the infection has been refractory to previous forms of treatment and multiple sites have been involved, daily doses up to 12 Gm. have been used.

For patients who are to receive cephapirin intravenously it is convenient to use the 1-Gm., 2-Gm., or the 4-Gm. vial (See Precautions).

Intermittent Intravenous Injection—The contents of the 1-Gm. vial should be diluted with 10 ml. or more of diluent and administered slowly over a 3- to 5-minute period or may be given with intravenous infusions.

The 2-Gm. vial should be diluted with Dextrose Injection, U.S.P. or Sodium Chloride Injection, U.S.P. When only 20 to 25 ml. are added, Sterile Water for Injection, U.S.P. may be used. The table below gives concentrations for various diluent volumes.

Diluent Added (ml.)	*Solution Concentration*	*Grams per ml.*
100	1 Gm. per 50 ml.	0.020
50	1 Gm. per 25 ml.	0.040
20	1 Gm. per 10 ml.	0.100

Intermittent Intravenous Infusion with Y-Tube—Intermittent intravenous infusion with a Y-type administration set can also be accomplished while bulk intravenous solutions are being infused. However, during infusion of the solution containing Cefadyl (sterile cephapirin sodium), it is desirable to discontinue the other solution. When this technique is employed, careful attention should be paid to the volume of the solution containing Cefadyl so that the calculated dose will be infused. When a Y-tube hookup is used, the contents of the 4-Gm. vial of cephapirin should be diluted by addition of 40 ml. of Sterile Water for Injection, U.S.P., 5 percent Dextrose Injection, U.S.P., or Sodium Chloride Injection, U.S.P.

Continuous Intravenous Infusion—After reconstitution, Cefadyl may be added to the solutions listed below under *Stability*. The choice of solution and volume should be dictated by the fluid and electrolyte management of the patient.

Stability. *Storage Stability:* After reconstitution, it is stable for 12 hours at room temperature or 10 days under refrigeration when reconstituted with Sterile Water for Injection, U.S.P. The pH of the resultant solution ranges from 6.5 to 8.5 During these storage conditions, no precipitation occurs. A change in solution color during this storage time does not affect the potency.

Compatibility with the Infusion Solutions: Cefadyl is stable and compatible for 24 hours at room temperature at concentrations between 2 mg./ml. and 30 mg./ml. in the following solutions:

Sodium Chloride Injection, U.S.P., 5% W/V Dextrose in Water, U.S.P., Sodium Lactate Injection, U.S.P., 5% Dextrose in Normal Saline, U.S.P., 10% Invert Sugar in Normal Saline, 10% Invert Sugar in Water, 5% Dextrose + 0.2% Sodium Chloride Injection, U.S.P., Lactated Ringer's with 5% Dextrose, 5% Dextrose + 0.45% Sodium Chloride Injection, U.S.P., Ringer's Injection, U.S.P., Lactated Ringer's Injection, U.S.P., 10% Dextrose Injection, U.S.P.

Supply. Cefadyl (sterile cephapirin sodium) for I.M. or I.V. Injection. Cephapirin sodium equivalent to 1 Gm., 2 Gm., or 4 Gm. cephapirin. NDC 0015-7628—1-Gm. vial. NDC 0015-7629—2-Gm. vial. NDC 0015-7630—4-Gm. vial.

For information on package sizes available, refer to the current price schedule.

BRISTOL

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*Bauer, A. W., Kirby, W. M. M., Sherris, J. C., and Turck, M.: Antibiotic Testing by a Standardized Single Disc Method, Am. J. Clin. Pathol., 45:493, 1966. Standardized Disc Susceptibility Test, FEDERAL REGISTER 37:20527-29, 1972.

Cancer of the Bile Ducts Associated with Ulcerative Colitis

ONYE E. AKWARI, M.D., JONATHAN A. VAN HEERDEN, M.D., ChB. (Cape Town), F.R.C.S. (C), WILLIAM T. FOULK, M.D., ARCHIE H. BAGGENSTOSS, M.D.

Thirteen patients with bile duct cancer (excluding gallbladder) and associated chronic ulcerative colitis (CUC) were seen at the Mayo Clinic from 1935 through 1973. Most patients had initial symptoms of severe diarrhea and bleeding, followed by a pattern of mild-to-moderate disease with exacerbations and remissions. Three patients had especially severe symptoms and underwent total colectomy (1 patient) or proctocolectomy (2 patients) an average of 15.7 years from onset of CUC symptoms. Anorexia, followed rapidly by the development of progressive jaundice (or a sudden deterioration when liver disease was already present), marked the onset of symptoms of bile duct cancer in the 13 patients. The overall mean duration from onset of CUC to development of symptoms of bile duct cancer was 19 years. The patients in whom colitis was managed by proctocolectomy or total abdominal colectomy developed symptoms of bile duct cancer an average of 9.4 years after colectomy. When cancer was diagnosed, the tumor had spread beyond the bile ducts in 10 patients. The tumors were difficult to identify and often infiltrated the hepatic hilus. The present series and review of the literature suggest that the relationship between CUC and bile duct cancer is more than a chance occurrence. The carcinoma has an onset approximately 3 decades earlier than does carcinoma of the bile ducts without CUC. Surgical removal of the diseased colon and mode of medical management of the unresected colon have no relationship to the subsequent development of carcinoma of the bile ducts; neither does the extent or severity of the colonic disease. The prognosis of carcinoma of the bile ducts unfortunately continues to be dismal.

HEPATIC DISEASE is one of the more reliably established extracolonic complications of ulcerative colitis. Early reports[5,28] of fatty liver or some form of cirrhosis were followed by reports of lesions that varied from mild triaditis without cholestasis to severe triaditis with cholestasis and progressing, in some instances, to cirrhosis of the liver.[2,31] Severe chronic, fibrosing inflammation in the larger bile ducts within as well as outside the liver, termed "sclerosing cholangitis,"[12,29,33] has a well-known association with ulcerative colitis. The "beaded" appearance of the bile ducts in sclerosing cholangitis is also well known. Coincidental, but apparently unrelated, obstructive diseases of the biliary tree have been described in patients with ulcerative colitis. These include patients who have bile duct stricture with and without gallstones[3,4,9,28] and choledocholithiasis.[5]

Since the report of primary carcinoma of the biliary tract in a review of autopsy material of ulcerative colitis,[22] 48 cases (excluding 3 cases previously reported from the Mayo Clinic) have been described with the rare coexistence of these two diseases.[1,2,6–8,10,11,13,17–19,21,24–27,33,35] Careful review of the evidence on bile duct cancer and chronic ulcerative colitis supports a non-random association between the two diseases.[2,6,24] Previous reports from the Mayo Clinic[31,32,34] have contributed cases to the literature in which there is an association of bile duct cancer with ulcerative colitis. The present report seeks to present in detail the Mayo Clinic experience from 1935 to 1973. The 13 Mayo Clinic cases reported on herein bring to 61 the total number of cases found in the English literature.

The Present Study

Material

This study concerns 13 patients with bile duct cancer (excluding the gallbladder) and associated ulcerative colitis who were seen at the Mayo Clinic from 1935 to 1973, inclusive (Tables 1, 2, and 3). Three of the patients were previously described (case 4[31]; cases 5 and 10).[34] All pa-

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Reprint requests: Dr. O. E. Akwari, c/o Section of Publications, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55901.

TABLE 1. *Clinical and Survival Data on 13 Mayo Clinic Patients With Bile Duct Cancer Complicating Chronic Ulcerative Colitis (CUC)*

Case	Sex	Age at Onset of Symptoms of CUC (yr)	Onset of Symptoms of CUC to Diagnosis of CUC (mo)	Age at Onset of Symptoms of Bile Duct Cancer (yr)	Onset of Symptoms to Diagnosis of Bile Duct Cancer (mo)	Onset of Bile Duct Cancer Symptoms to Death (mo)
1	M	22	16.8	41	15	31.3
2	M	23	97.9	32	4.4	7.0
3	M	31	101.2	62	6.8	7.4
4	M	14	4.9	30	23.9	23.9
5	M	7	14.7	23	6.4	12.9
6	F	9	0	41	0.1	12.7
7	F	27	0	54	3	9.2
8	M	9	0	32	5.5	7.0
9	M	21	36	37	1.6	42.1
10	M	17	6	34	1.7	7.3
11	F	18	0	33	7.8	47.5
12	M	36	84	43	4.5	8.3
13	M	15	0	35	13.1	27.2
Mean		19	27.8	38	7.2	18.8

tients had ulcerative colitis that was firmly established by combinations of clinical, endoscopic, roentgenographic, and pathologic evidence. Histologic evidence of cancer of the bile ducts was also available. Twelve of the 13 patients underwent surgery, and carcinoma of the bile ducts was demonstrated in 11. Of the remaining two patients, one had severe liver disease for 4 years and was never a suitable surgical candidate; severe cirrhosis and a large ductal type carcinoma were found at autopsy. The other patient underwent surgical exploration,

TABLE 2. *Ulcerative Colitis History of 13 Mayo Clinic Patients With Bile Duct Cancer and Associated Chronic Ulcerative Colitis (CUC)*

Case	Extent	Activity of CUC	Extracolonic Manifestations of CUC	Treatment
1	Entire colon & rectum	Moderate	None	Emetine
2	Entire colon & rectum	Mild	None	Sulfa drugs
3	Entire colon	Mild	Arthritis, skin lesions	Sulfa drugs
4	Entire colon & rectum	Moderately severe	Pyoderma gangrenosum, iritis, hepatic portal triaditis	Vaccine, sulfa drugs, blood transfusions
5	Entire colon & rectum	Moderate	Pyoderma & other skin lesions	Blood transfusions & steroids when jaundice supervened
6	Entire colon & term. ileum	Severe	None	Proctocolectomy
7	Entire colon, rectum, & term. ileum	Severe	Pyoderma gangrenosum, history of jaundice 15 yr before onset of bile duct cancer	Proctocolectomy
8	Term. ileum & entire colon	Moderate	None	Bismuth nitrate & blood transfusions
9	Term. ileum, entire colon, & rectum	Moderately severe	None	Total colectomy, ileorectostomy; rectal & term. ileal disease; managed with steroids postcolectomy
10	Splenic flexure & transverse colon	Mild	None	Sulfanylguanidine
11	Entire colon	Moderate	None	Steroids, sulfa drugs, blood transfusions
12	Entire colon & term. ileum	Mild	Skin lesions	Paregoric
13	Entire colon & rectum	Very mild	None	Diet only

TABLE 3. *Pathologic Changes in 13 Mayo Clinic Patients With Bile Duct Cancer Complicating Chronic Ulcerative Colitis*

	Cancer				
Case	Grade	Type	Gross Character	Location	Metastases at First Diagnosis
1	1	Papillary adenocarcinoma	Confined to duct wall	Lower ⅓ common bile duct	No
2	3	Adenocarcinoma	Nodular mass infiltrating liver hilus	Upper ⅓ common bile duct	Yes
3	2	Scirrhous adenocarcinoma	Nodular extraductal mass	Confluence of rt and lt hepatic bile ducts	Yes
4	—	Ductal type, adenocarcinoma	Nodular mass infiltrating liver hilus	Hepatic ducts at liver hilus	Yes
5	2	Adenocarcinoma	Infiltrating liver hilus	Confluence of rt and lt hepatic ducts	Yes
6	1	Scirrhous adenocarcinoma	Infiltrating liver hilus	Confluence of rt and lt hepatic ducts	Yes
7	3	Adenocarcinoma	Infiltrating liver hilus	Confluence of rt and lt hepatic ducts	Yes
8	2	Papillary adenocarcinoma	Infiltrating liver hilus	Rt intrahepatic bile duct	Yes
9	2	Papillary adenocarcinoma	Confined to duct wall	Middle ⅓ common bile duct	No
10	1	Adenocarcinoma	Infiltrating liver hilus	Common hepatic duct	Yes
11	2	Scirrhous adenocarcinoma	Infiltrating liver hilus	Confluence of rt and lt hepatic ducts	Yes
12	2	Scirrhous adenocarcinoma	Infiltrating liver hilus	Lower ⅓ common bile duct	Yes
13	2	Adenocarcinoma	Infiltrating liver hilus	Lt intrahepatic duct	No

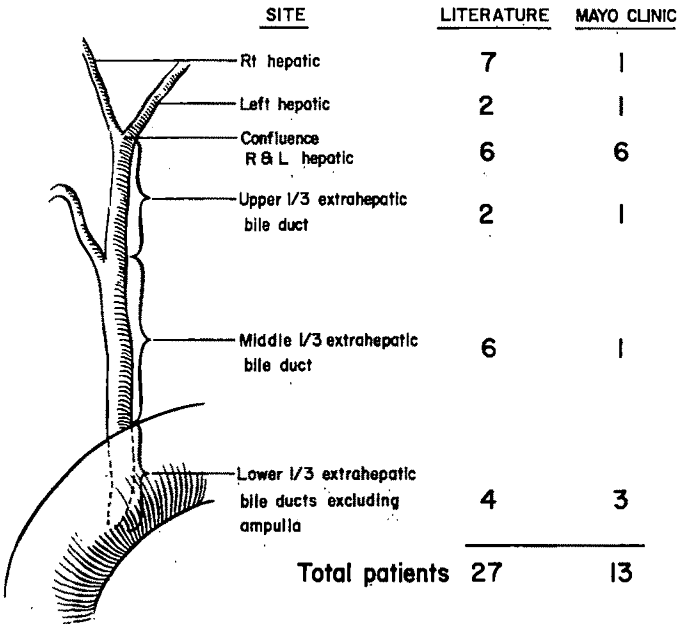
SITE LITERATURE MAYO CLINIC
Rt hepatic 7 1
Left hepatic 2 1
Confluence R & L hepatic 6 6
Upper 1/3 extrahepatic bile duct 2 1
Middle 1/3 extrahepatic bile duct 6 1
Lower 1/3 extrahepatic bile ducts excluding ampulla 4 3
Total patients 27 13

FIG. 1. Anatomic location of tumor in 40 cases of chronic ulcerative colitis associated with bile duct cancer.

which revealed no mechanical cause of biliary tract obstruction, but a carcinoma was found in the right intrahepatic bile duct at autopsy.

Incidence

From 1935 to 1973, inclusive, of the 32,300 autopsies performed at the Mayo Clinic, 120 revealed bile duct cancers, an incidence at autopsy of 0.37%. Two of the patients with cancer of the bile ducts also had ulcerative colitis, making the autopsy incidence of bile duct cancer

TABLE 4. *Patients With Cancer of the Bile Ducts Complicating Ulcerative Colitis (CUC) Who Had Previous Proctocolectomy or Total Abdominal Colectomy*

Case	Age at Onset of CUC (yr)	Onset of CUC to Colectomy (yr)	Duration from Colectomy to Onset of Bile Duct Cancer Symptoms (yr)
6	9	18.2	14.3
7	27	18.1	9.0
9	21	10.9	5
Mean	19	15.7	9.4

TABLE 5. *Review of Eight Patients With Liver Disease Secondary to Chronic Ulcerative Colitis (CUC) Prior to Development of Bile Duct Cancer*

Reference	Age at Onset of CUC (yr)	Age at Onset of Liver Disease (yr)	Age at Onset of Symptoms of Bile Duct Cancer (yr)	Hepatic Pathology
Boden et al.[2]	44	45	55	Pericholangitis
Rankin et al.[24]	46	46	52	Cholestasis
Thorpe et al.[33]	30	30	41	Portal fibrosis and inflammation, peripheral cholestasis
Ham[14]	16	18	22	Cholangitis and biliary cirrhosis
Morowitz et al.[18]	12	12	—	Active progressive cirrhosis with biliary and postnecrotic features (colectomy at age 28 yr)
Ross[27] and Braasch	34	40	51	—
Ross and Braasch[27]	30	30	46	Cholestasis; (?) biliary calculi (colectomy at age 34 yr)
Present series (case 4)	14	26	30	Portal triaditis
Mean	28	30	42	

associated with ulcerative colitis 0.0062% of all autopsy cases or 1.6% of autopsy cases of bile duct cancer.

Ulcerative Colitis

The mean age of our patients at onset of ulcerative colitis (Table 1) was 19 years, with a range of 7-36 years. The average duration of symptoms to diagnosis of chronic ulcerative colitis was 27.8 months. The onset of ulcerative colitis in all 13 of our patients was marked by severe diarrhea. In seven patients, the diarrhea was associated with severe hemorrhage requiring multiple blood transfusions. Skin lesions were present in five patients, including three with pyoderma gangrenosum; one had iritis and one had joint manifestations. One patient had a perineal fistula. No patients had abscess, colonic obstruction, or toxic megacolon.

After initial severe symptoms, most patients developed a pattern of mild-to-moderate disease with exacerbations and remissions (Table 2). One patient (case 4) had ulcerative colitis complicated by liver disease. Mild portal triaditis was present on liver biopsy 4 years preceding the onset of symptoms referable to bile duct cancer. An additional patient (case 7) had a history of post-transfusion jaundice, with apparent complete recovery 15 years prior to the onset of symptoms of bile duct cancer.

In 10 patients, the ulcerative colitis was managed by various regimens (Table 2) aimed at symptomatic relief and support. In three patients, proctocolectomy (cases 6 and 7) or total colectomy (case 9) was done because of severe symptoms. In these patients, symptoms of ulcerative colitis had been present for an average of 15.7 years before colectomy was undertaken (Table 4). The one patient (case 9) in whom bowel continuity was reestablished by ileorectostomy after total abdominal colectomy continued to be symptomatic from recurrent ileal and rectal disease but responded satisfactorily to steroid therapy.

In one patient (case 6), ulcerative colitis was complicated by colonic cancer, which was discovered in the resected specimen at proctocolectomy 14.3 years prior to the onset of symptoms of bile duct cancer.

Bile Duct Cancer

The mean age at onset of symptoms of bile duct cancer was 38 years with a range of 23-62 years (Table 1). The average duration from onset of ulcerative colitis symptoms to onset of symptoms referable to bile duct cancer was 19 years. The patients (cases 6, 7, and 9) whose colitis was managed by proctocolectomy or total abdominal colectomy developed symptoms of bile duct cancer 14.3, 9, and 5 years, respectively, after the colon was removed. Mode of management of colitis did not seem to make any difference in the pattern of disease leading up to bile duct cancer.

The onset of bile duct cancer was insidious in all cases. The most frequent presentation was fatigue, loss of weight, and anorexia; these were followed rapidly by the development of acholic stools, dark urine, pruritus, and progressive jaundice. Pain was a feature in 11 patients.

The most common findings on initial physical examination were icterus (12 patients) and hepatomegaly (10 patients).

Initial bilirubin determinations were made in 11 patients. The direct bilirubin levels ranged from 0.7 to 19.1 mg/dl, with a mean of 9.7 mg. Total bilirubin ranged from 1.3 to 28.5 mg/dl, averaging 13.0 mg. The serum alkaline phosphatase level measured in nine patients ranged from 148 to 991 units/liter and averaged 530 units. Six of the nine patients had presenting alkaline phosphatase levels that were higher than 400 units.

Roentgenographic examination of the upper gastrointestinal tract was obtained in eight cases and revealed unequivocal abnormalities in four. Transhepatic cholangiography was done prior to surgical exploration in four patients and was interpreted as showing obstruction or filling defects (or both) of the biliary tract in all four.

Surgical Experience

Five patients had undergone previous surgical explorations 4-8 months before coming to our clinic. These procedures included a positive exploration and diagnosis of cancer in one and negative explorations in four. Three of the five patients underwent cholecystectomy for presumed noncalculous gallbladder disease.

In all, 12 patients underwent surgical exploration at our clinic, and a diagnosis of cancer was established in 11. Ten of the 11 patients had the diagnosis of cancer established at exploration, and the surgical procedure was diagnostic or palliative only, because of the presence of metastasis.

Palliative resection of tumor with a duct-enteric anastomosis over a stent was done in one patient, a bypassing duct-enteric anastomosis in one, a common duct exploration and T-tube decompression in three, and a common duct exploration with a stent through a malignant stricture in one. In four patients, the procedure consisted of biopsy of inoperable lesions.

Only one patient (case 1) was considered suitable for curative resection. This patient had a small tumor confined entirely to the common bile duct in its distal third. The tumor was resected, and a common bile duct-duodenal anastomosis was performed. The patient was one of the longer survivors (31.3 months).

Pathologic Features

The gross pathologic features of ulcerative colitis found in these patients are summarized in Table 2. In all cases, strict attention was paid to differentiating the pathologic changes in these patients from those of granulomatous (Crohn's) disease.

The anatomic distribution, histologic types, and estimates of degree of anaplasia (Broders' classification) were noted in all 13 patients (Fig. 1, Table 3). Histologically, all patients had adenocarcinomas, and the scirrhous and papillary types were the most frequent.

At the first diagnosis of cancer, the tumor had spread beyond the bile duct in 10 patients. Moreover, these tumors were difficult to identify, often infiltrating the hepatic hilus and extending into the intrahepatic bile duct branches. These factors restricted aggressive surgical intervention.

Associated cholelithiasis was not present in any of the patients.

Other Therapeutic Measures and Survival

In five patients (cases 6, 9, 11, 12, and 13), adjuvant chemotherapy was administered. Two patients (cases 6 and 9) were also given high-dose radiation therapy. One patient (case 2) received radiation therapy alone.

The length of survival, measured as the duration from onset of symptoms of bile duct cancer to death, revealed a range of 7.0-47½ months, with a mean of 18.8 months (Table 1).

The complications of biliary tract malignancy occurring in these patients were typical for the disease.[16,20,23,34] Obstructive jaundice eventually developed in all 13 patients and was associated with hepatomegaly in 12 and full-blown hepatic decompensation and coma in 4. Ascites was present in three of the patients. One patient died of esophageal variceal bleeding. Cholangitis was a complication in 11 and was associated with bacteremia in 7 of the 11 patients. Metastases were most common to the liver (9 patients) and regional lymph nodes (9 patients).

The more common terminal event followed a characteristic pattern: hepatic failure, sepsis, shock, renal shutdown, and death.

Discussion

The incidence of cancer of the bile ducts at autopsy has been reported as 0.26%[16] to 0.54%,[23] whereas the operative incidence has been reported as 0.5%[20] to 1.4%[14] of all operations on the biliary tree. Keogh,[15] in 1964, estimated that, in the Australian state of Victoria, bile duct tumors have an annual incidence in the population of 0.8 per 100,000 (0.0008%).

The incidence of bile duct cancer in patients with ulcerative colitis has been estimated at between 0.4%[6] and 1.4%.[26] These comparatively alarmingly high occurrence rates emphasize an association between the two diseases. Of 48 cases in the literature, 33 were detailed enough to permit general statements. Sex was specified in 26 cases: 18 males and 8 females. Age at onset of ulcerative colitis ranged between 7[24] and 54 years,[27] with a mean of 25 years and a standard deviation of 12 years in the 28 cases in which the age at onset of ulcerative colitis was specified.

Most patients had severe disease initially manifested by bloody diarrhea and abdominal pain. Five patients[18,21,27] had joint, eye, and skin stigmata of ulcerative colitis. At onset of bile duct cancer symptoms, most of the patients had only mild-to-moderate intermittent exacerbations of their bowel disease. One patient[3] had no symptoms of colitis and had been completely free of symptoms during the preceding 9 years.

Seven patients[2,11,18,24,27,33] had proved preexisting liver disease, presumably secondary to ulcerative colitis. Liver disease of varying severity had been present from 4[11] to 16 years,[27] with a mean of 8.9 years (Table 5). One patient[24] also had carcinoma of the colon.

In most of the patients, the colonic disease was managed medically. Treatment consisted generally of blood transfusions, sulfonamide drugs, and steroid preparations. In 19 reported cases,[6,10,18,21,24–27] colectomy or proctocolectomy was performed for definitive management of ulcerative colitis. All of these patients had severe symptoms or complications (or both) of ulcerative colitis. The most common complications were hemorrhage, uncontrolled diarrhea, and malnutrition. Colectomy was done in one case[18] as a last resort to halt progressive liver disease and in another case[27] because of spontaneous colonic perforations.

The onset of bile duct cancer was, in the great majority of cases, clearly delineated by a dramatic change in the clinical course. The most common early manifestations were malaise, anorexia, fever, and right upper quadrant and epigastric pain. Subsequently, jaundice developed in all reported patients.

The age at onset of symptoms of bile duct cancer in 24 patients ranged from 20[10] to 73[27] years, with a mean of 40 years and standard deviation of 13 years. Bile duct cancer occurred not only in patients treated medically for ulcerative colitis but also many years after colectomy or proctocolectomy.

In 16 patients whose chronic ulcerative colitis was managed medically, the mean age at onset of symptoms of ulcerative colitis was 29 years (range of 14-46 years and standard deviation of 10 years). Fourteen of the 16 developed symptoms referable to bile duct cancer at a mean age of 41 years, with a range of 22 to 53 years and a standard deviation of 9 years.

TABLE 6. *Time of Surgery in Relation to Subsequent Cancer Development in Patients With Chronic Ulcerative Colitis (CUC) and Bile Duct Cancer*

Series	No. of pts	Mean age at Onset CUC, yr	Mean Interval, yr CUC to Colectomy	Mean Interval, yr Colectomy to Bile Duct Cancer
Previous Reports	10*	22	10	8
Mayo Clinic	3	19	16	9
Overall	13	21	11	8
(Range)		(7-54)	(2-22)	(1-20)

*From a group of 19 patients in whom CUC was managed by removal of diseased colon; complete data were not available on 9 of the 19 patients.

In 10 patients undergoing colectomy (Table 6), the average age at colectomy was 32 years (range of 18-66 years and standard deviation of 13 years). In these 10 patients,[6,10,24,26,27] symptoms referable to cancer of the bile ducts developed at a mean age of 40 years (range 20-73 years and standard deviation of 17 years).

Clinical examination was not helpful in the diagnosis. Although it was common to attribute the icterus to liver disease of ulcerative colitis, most of the patients were extremely ill. Stauffer[30] has commented that these patients are generally more gravely ill than is the average patient with liver disease of ulcerative colitis.

Of 24 reported patients who eventually underwent exploratory laparotomy, 17 had positive diagnosis of cancer made at exploration. Thirteen patients (76.5% of those in whom cancer was found) already had metastasis at the initial diagnosis. In four patients, no cause was found at exploration for obstructive jaundice, and in the remaining three patients, strictures involving the proximal bile ducts were found but were thought to be benign.

For more than 25% of the patients, the diagnosis of cancer of the bile ducts was not made during life.

The average survival time from onset of symptoms to death from bile duct cancer and its complications was 11 months (range of 1.5-54 months and median 6.0 months). Only one patient[17] was considered to be a suitable candidate for curative resection; pancreatoduodenectomy was performed for a common bile duct lesion, and the patient survived 48 months.

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Primary Peritonitis in Infancy and Childhood

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Primary peritonitis, rarely diagnosed preoperatively, is an uncommon disease accounting for 2.1% of all pediatric abdominal emergencies. It is often associated with urinary or hepatic pathology, the former the source of the infecting organism in the majority of cases, and presents with characteristic symptoms depending upon whether it occurs in infancy or childhood. The symptoms and signs which allow for a positive prospective diagnosis are illustrated by comparing this disease to those entities with which it is most often confused, e.g. diffuse peritonitis of other etiologies, and include a short duration of symptoms, associated urinary tract infection and an absence of free air on abdominal roentgenograms. In the past, gram positive organisms were the most common infecting agent; however, in this series gram negative bacteria accounted for 69% of the organisms. Antibiotics with a gram negative spectrum and exploratory laparotomy with appendectomy are the hallmarks of therapy, the latter replaced by abdominal tap only in the patient who satisfies the criteria for primary peritonitis and in whom an associated disease makes the risk of surgery prohibitive.

PRIMARY PERITONITIS, a diffuse peritoneal infection without an apparent intra-abdominal source, is an uncommon disease, infrequently considered in the differential diagnosis of peritoneal sepsis and rarely diagnosed preoperatively. In the early part of this century it comprised approximately 10% of all pediatric abdominal emergencies,[2] however, recently incidences of less than 1—2% have been reported.[3,5] The cases of primary peritonitis seen at our institutions in the past ten years indicate that significant changes have occured in this disease both clinically and bacteriologically and that a correct preoperative or premortem diagnosis can be made if specific clinical and laboratory findings are carefully evaluated. Since difficulties in distinguishing it from other acute abdominal emergencies invariably occur, all patients admitted with peritoneal sepsis were included in the study to illustrate those findings which are diagnostic for primary peritonitis.

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Material

A review of 84,352 pediatric admissions to two large metropolitan hospitals for the past ten years revealed 26 patients with primary peritonitis and 157 patients with diffuse peritoneal sepsis of other etiologies (Table 1). All diagnoses were confirmed either by autopsy, exploratory laparotomy or abdominal tap. Excluded from the study were cases in which peritonitis was a result of a previous operative procedure or trauma.

The patients are divided into two groups according to age: the first two years of life or infancy and 2–14 years of age or childhood. There were 34 cases of peritoneal sepsis in infancy, six of whom had primary peritonitis and 149 cases of peritonitis in childhood, twenty of whom had the primary variety.

Clinical and Laboratory Findings

Primary peritonitis accounts for 2.1% of all pediatric abdominal emergencies admitted to our hospitals; however, if only those patients with diffuse peritonitis are considered the incidence is 17.6% in infancy and 13.4% in childhood. The sex and age distribution of all forms of pediatric peritonitis are illustrated in Fig. 1. Primary peritonitis in infancy occurred in the first two months of life with females predominating 2:1; however, in childhood a peak incidence from 5 to 9 years with an average of 8.4 years and a sex ratio of 1.2 females to 1 male occurred. Peritonitis of other etiologies in infancy generally occurred in the first five days of life with a sex

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TABLE 1. *Etiology of Peritonitis in Infants and Children (183 patients)*

Primary Disease	Infants	Children
Primary Peritonitis	6	20
Spontaneous Enteric Perforation		
Stomach	10	
Duodenum (ulcer)		1
Jejunum	3	
Ileum	7	1
Sigmoid	2	
Meconium Peritonitis	1	
Pancreatitis with Ruptured Pseudocyst	1	
Subhepatic Abscess	1	
Infected Omphalomesenteric Cyst	1	
Pelvic Inflammatory Disease with Diffuse Peritonitis		4
Ruptured Appendix	2	123
Total	34	149

distribution of 1.2 females: 1 male; whereas, in childhood the peak incidence occurred from 7 to 10 years with an average age of 8.5 years and a sex ratio of 1:1.4, females: males.

The signs of primary peritonitis in infancy developed over a one to two day period and began with the manifestations of sepsis, i.e. poor feeding, lethargy, fall in temperature and reduced platelet count and culminated in a distended abdomen which felt doughy to palpation. In three of the six patients, peritonitis was preceded by an extensive pneumonia before signs of sepsis became apparent. Peritonitis of other etiologies in the first two years of life generally presented as a catastrophic event evolving over a period of hours. These patients generally presented with one or all of the following: lethargy or irritability, apnea, no evidence of prior infection, abdominal rigidity and/or abdominal distention.

The clinical presentation in children differed from that observed in infants. The symptoms of abdominal pain, nausea, vomiting and diarrhea and the findings of diffuse abdominal tenderness, rectus spasm, abdominal rigidity, rebound tenderness and diffuse tenderness on rectal examination occurred with equal frequency in both patients with primary peritonitis and those with peritonitis of other etiologies. The time from the onset of symptoms to the presentation of abdominal findings was 21.5 hours with a span of 6–60 hours for patients with primary peritonitis and differed significantly from 8.2 days (median of 3 days) with a range of 12 hours to 90 days for peritonitis of other causes ($p<.02$). If patients with cirrhosis and nephrosis in whom the development of primary peritonitis often is insidious[1] are excluded, the abdominal findings described occurred in 15.8 hours with a range of 6–24 hours.

There was no significant difference in temperature between those with primary peritonitis and those with diffuse peritonitis of other etiologies in either infancy (both groups averaged 36 C) or childhood (38.4 and 38.5 respectively). White blood count was also not significantly different in the two groups. In infancy patients with

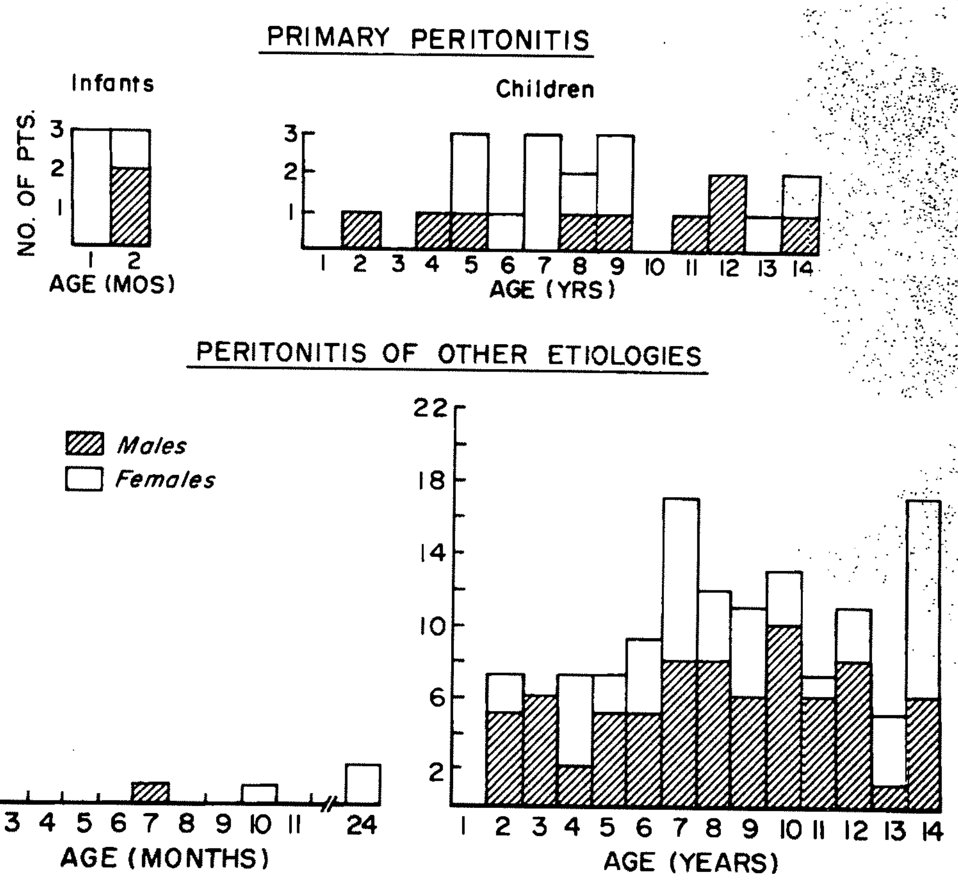

FIG. 1. Age and sex distribution of infants and children with primary peritonitis compared to those with peritonitis of other etiologies.

TABLE 2. *Pathogens Isolated from Peritoneal Cultures in Patients with Primary Peritonitis (26 pts) and in those with Peritonitis of Other Etiologies (157 pts)*

Pathogen	Primary Peritonitis	Peritonitis of Other Etiologies
E. coli	11	96
Pseudomonas	2	15
Aerobacter aerogenes	1	19
Klebsiella	1	5
Paracolon	1	1
Proteus	1	1
Bacteroides		2
Neisseria		4
Total Gram Negative Cultures	17	143
Streptococcus	5	23
Pneumococcus	4	3
Staphlococcus		5
Clostridium perfringens		1
Diptheroids		1
Total Gram Positive Cultures	9	33
No growth		12
No culture	2	8

primary peritonitis had an average WBC of 7.2 with a range of 5.5–10.5 compared to an average of 10.5 with a range of 4.7–30.0 for peritonitis of other etiologies. In childhood patients with primary peritonitis had an average WBC of 16.2 (3.8–29.0) vs. 17.5 (1.2–45.0) for peritonitis of other causes. In infancy there was no difference in urine analysis between the two groups; however, in childhood 10% of the patients with primary peritonitis had acetone and 78% had 5 or more WBC's/hpf whereas 50% of those with peritonitis of other etiologies had acetone and 40% had 5 or more WBC's/hpf ($p<.01$).

Abdominal roentgenograms showed a nonspecific pattern with an occasional air filled loop of small bowel in patients with primary peritonitis in both infancy and childhood. In infants with peritonitis of other etiologies abdominal x-rays were most helpful since 21 of 22 patients with enteric perforations demonstrated free air and one patient with meconium peritonitis showed calcifications. In childhood appendicoliths occurred in 13% of patients with ruptured appendicies and free air was seen in one case of perforated duodenal ulcer and one patient with a perforated appendix. There were 6 of 28 patients in infancy and 139 of 157 patients in childhood with diffuse peritonitis whose abdominal roentgenograms were indistinguishable from patients with primary peritonitis.

The etiology of diseases causing diffuse peritonitis in this series are illustrated in Table 1. The diagnosis of primary peritonitis was made by autopsy in six, abdominal tap in three (all patients with primary peritonitis and either chirrhosis or nephrosis), and in the remainder by exploratory laparotomy.

The organisms responsible for peritoneal sepsis are illustrated in Table 2 and demonstrate that gram negative pathogens occur most frequently with *E. coli* the most common offending organism. Associated infections in infants with primary peritonitis were common: three of six patients had extensive pneumonias, whereas only one of 28 patients with peritonitis of other etiologies had an associated infection (urinary tract). In childhood two of twenty patients with primary peritonitis had upper respiratory tract infections, one of whom grew the same organism in the sputum as cultured from the peritoneum; ten patients had urinary tract infections, nine of whom grew the same organisms from their peritoneum as isolated from the urine; and two had a vaginal discharge both of which cultured the same organism isolated from the peritoneum. In patients with peritonitis of other etiologies, 2 of 157 had upper respiratory infections, one of whom had the identical organism cultured from the sputum and appendiceal stump and one had a urinary tract infection in which the urine culture grew the same organism as isolated from the peritoneum.

Table 3 shows that the nephrotic syndrome, post necrotic cirrhosis and urinary tract infections are frequently found in the pediatric patient with primary peritonitis. Urinary pathology occurs in 58% of these patients and accounts for 71% of the associated diseases.

Three patients with primary peritonitis in infancy died giving a mortality of 50%. The other three patients survived without any significant complications. A 39% mortality was found for infants with peritonitis of other etiologies and compares favorably to that reported by others. Complications which occurred in the survivors in this group included one case of disseminated intravascular coagulopathy, one subhepatic abscess and one prolonged ileus. In children with primary peritonitis three of twenty died for a mortality of 15%. Complications of those surviving included three cases of postoperative pneumonia and one pleural effusion. There was one death in 157 patients with peritonitis of other causes. Complications of the survivors included four subphrenic abscesses, three pelvic abscesses, three major wound abscesses, two postoperative pneumonias, one pelvic cellulitis and one bowel obstruction. All patients explored had appendectomies and eight of this group had their peritoneal cavity drained. There was no difference in mortality between those patients who had drains placed and those who did not.

TABLE 3. *Associated Disease in Infants and Children with Primary Peritonitis*

Associated Disease	Infants	Children
Nephrotic Syndrome		4
Post necrotic cirrhosis		3
Hydronephrosis		1
Urinary Tract Infection		10
Hyaline Membrane Disease	1	
Cystic Fibrosis		1
Adrenogenital Syndrome		1

Discussion

Primary peritonitis is an uncommon disease accounting for 2.1% of patients presenting with an acute abdominal emergency. If it is to be placed in proper perspective, however, it must be compared to those entities in which a similar pathologic process occurs, i.e. diffuse peritoneal sepsis, and hence those diseases from which it is most difficult to differentiate. In this setting the incidence rises to 17.6% in the infant and 13.4% in the child.

The correct preoperative diagnosis can be made with reasonable assurity by noting several diagnostic features. Primary peritonitis in infants develops over a one to two day period, is usually preceded by an overwhelming infection and demonstrates non specific findings on abdominal roentgenograms. Peritonitis of other etiologies in infants has a rapid onset which occurs in a period of hours and is not preceded by infection. Abdominal x-rays are helpful in the latter group since free air or calcifications are almost always observed. Temperature, white blood count, urine analysis and physical examination are usually not helpful in distinguishing between the diseases.

In the child who presents with abdominal findings of diffuse peritonitis occurring in less than 24 hours from the onset of symptoms without a mass or free air on abdominal roentgenograms and who gives a history of nephrosis, post necrotic cirrhosis or urinary tract infection or demonstrates bacteriuria, pyuria and a urine free of acetone should be highly suspect of primary peritonitis. Temperature and white blood count, although reported to be most helpful[1,3,6] were not significantly different in the two groups. There was a slight predilection for the female in primary peritonitis whereas peritonitis of other etiologies favored the male; however, however, neither the sex ratio or age incidence were diagnostic.

The significance of the duration of symptoms in a patient with abdominal findings of diffuse peritonitis is illustrated by the finding that 23 of 26 patients with primary peritonitis had symptoms for less than 24 hours whereas only 2 of 157 patients with peritonitis of other causes presented in a similar period of time. Acetone, an indication of the period of starvation, occurs in 10% of patients with primary peritonitis and 50% of those with peritonitis of other etiologies and is a reflection of the short time course in this disease. Pyuria occurred in many patients with peritonitis of other etiologies and was usually sterile whereas in those with primary peritonitis it was often associated with bacteriuria.

Gram negative organisms have become predominent in a disease which was once almost the exclusive domain of the gram positive bacteria. In the early part of this century Ladd and Gross[7] noted that gram negative infections were rare, the pneumococcus accounting for 50% or more of the offending organisms. Fowler[3] in 1971 reported that in New Zealand the hemolytic streptococcus was the most prevalent organism. In this series *E. coli* accounts for 42% of the pathogens with gram negative organisms comprising 69% of the total infecting agents (Table 2).

The origin of the infecting organism has been a point of major controversy. Four sources are generally cited: 1) blood; 2) genital; 3) transdiaphragmatic lymphatics; and 4) transmural migration through the gut wall.[4-8] In this study 15 patients or 58% of those with primary peritonitis had urinary tract disease. Since the same organism isolated from the peritoneum was also isolated from the urine in 9 of these patients, three of whom had the same organism cultured two to four months prior to the development of peritonitis, the urinary tract must be considered a likely source suggesting that an intimate relationship exists between it and the peritoneal cavity. Regardless of the primary etiology of the infecting organism, it is evident that urinary pathology often precedes or accompanies primary peritonitis and that a smear of spun urine may be helpful in suggesting the correct diagnosis and proper choice of antibiotic therapy.

Placed in proper perspective, primary peritonitis constitutes a significant proportion of cases of diffuse peritonitis and should be actively entertained in the child with generalized peritoneal signs developing in less than 24 hours, non specific roentgenograms, and a history of current or remote urinary tract infection. Such a patient should have sputum, urine and rectal cultures as well as microscopic examination of stained urine and sputum specimens before antibiotics are administered. A rational choice as to the appropriate antibiotic may then be made and following establishment of blood levels, exploration, gram stain of the peritoneal pus, appendectomy and peritoneal lavage should be peformed. We prefer not to drain the abdominal cavity since it has little advantage with the disadvantage of increasing morbidity. Abdominal tap should be reserved only for seriously ill patients who are poor risks because of cirrhosis or nephrosis and in whom the diagnostic findings which we have elaborated are satisfied.

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Amylase Clearance in Differentiating Acute Pancreatitis from Peptic Ulcer with Hyperamylasemia

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Thirty-four patients with abdominal pain, tenderness, and hyperamylasemia suggesting acute pancreatitis were studied prospectively to elucidate the relationship between peptic ulcer disease and pancreatitis. Confirming evidence of pancreatitis and/or ulcer was obtained either at laparotomy or by upper gastrointestinal roentgenograms. The presence or absence of pancreatitis was substantiated by measurement of the amylase/creatinine clearance ratio, which is significantly higher ($p < 0.001$) in patients with acute pancreatitis (9.3 ± 0.9), than in patients without pancreatitis (3.1 ± 0.2). Nine of the 34 patients were found to have gastric or duodenal ulcers. However, seven of the nine, despite an elevated serum amylase, had no sign of pancreatitis at surgery, on radiological examination, or by elevation of the amylase/creatinine clearance ratio (3.1 ± 0.4). It is suggested that hyperamylasemia associated with peptic ulcer disease is most often not indicative of acute pancreatitis and that treatment is most appropriately directed at the ulcer.

PEPTIC ULCER DISEASE has been accepted as one of the etiologic causes of acute pancreatitis.[3] The diagnosis of pancreatitis in such patients rests in part on the presenting clinical features, but is most influenced by elevations of serum amylase and lipase.[1,11,13] These indices, however, are not specific for pancreatitis,[1,4,15] and the symptoms and signs of acute pancreatitis may be identical with those of a penetrating ulcer.

The renal clearance of amylase, expressed as a percentage of creatinine clearance (the amylase/creatinine clearance ratio), rises in acute pancreatitis[12] and appears to be specific for that disease.[14] Using the amylase/creatinine clearance ratio, we have studied a group of patients with upper abdominal pain and hyperamylasemia, thought initially to be due to pancreatitis, who were found to have underlying ulcer disease. Our findings suggest that much of what is called pancreatitis secondary to an ulcer is not pancreatitis at all.

Material and Methods

The 34 patients in this study were selected from a 9-month prospective study of pancreatitis at the Massachusetts General Hospital. All patients had abdominal pain, tenderness, and an elevated amylase[10] consistent with acute pancreatitis. The admitting diagnosis in each case was pancreatitis. The diagnosis of peptic ulcer disease was later made in nine by upper gastrointestinal barium studies performed within one week of admission. To evaluate the presence or absence of genuine pancreatitis, the findings at surgery within ten days of admission, the clinical course, and the radiographic picture were compared with the amylase/creatinine clearance ratio, determined by a modification[14] of the method of Levitt, Rapoport and Cooperband.[12]

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$$\frac{\text{Amylase clearance (\%)}}{\text{Creatinine clearance}} = \frac{\dfrac{[\text{urine amylase}]}{[\text{serum amylase}]} \times \text{urine volume per unit time}}{\dfrac{[\text{urine creatinine}]}{[\text{serum creatinine}]} \times \text{urine volume per unit time}} \times 100$$

$$= \frac{[\text{Urine amylase}]}{[\text{serum amylase}]} \times \frac{[\text{serum creatinine}]}{[\text{urine creatinine}]} \times 100$$

Since the factors of urine volume and collection time cancel out of the equation, the clearance ratio, expressed as a percentage, can be calculated simply from the concentrations of amylase and creatinine in serum and urine samples obtained simultaneously.

Analyses of statistical significance utilized the standard error of the mean, standard deviation, and Student's t test.[9]

Results

By the use of clinical criteria (hospital course, evidence of pancreatitis or ulcer on upper GI series, and findings at surgery) the 34 patients were tentatively separated into three groups.

Group I. (25 patients): These patients had a protracted course of illness consistent with acute pancreatitis as well as evidence of pancreatitis either on upper GI series or at surgery. None were found to have a peptic ulcer. Their pancreatitis was associated with common duct stones (13), alcoholism (8), and hyperlipemia (4).

Group II. (seven patients): Although pancreatitis was the initial diagnosis in these patients, largely because of a high serum amylase and epigastric tenderness, all had rapid resolution of pain and did not have other evidence of pancreatic inflammation (fever, leucocytosis, hypovolemia). The diagnosis of peptic ulcer disease (duodenal—four, gastric—two, both—one) without concomitant pancreatitis was made both radiologically and at surgery in four patients, and by upper GI series alone in three. None of the ulcers had perforated.

TABLE 1. *Laboratory Values in the Three Groups*

	Normals (n = 46)	Group I (n = 25)	Group II (n = 7)	Group III (n = 2)
Serum amylase	4 - 25 Russell Units/ml	223 (± 41)	265 (±135)	1,205
Urinary amylase	< 100 Russell Units/ml	1,287 (± 265)	1,379 (± 892)	1,350
Serum lipase	< 2 units/ml	5.7 (± 0.5)	3.9 (± 2.0)	6.5
Amylase/ creatinine clearance	3.1 (± 0.2)	9.3* (± 0.9)	3.1 (± 0.4)	8.1

*$p < 0.001$ Group I vs. Group II
Group I vs. Normals
Figures in parenthesis = standard error of the mean.

Group III. (two patients): These patients had duodenal ulcers demonstrated by upper GI series, marked widening of the duodenal sweep indicating pancreatic swelling, and duodenal mucosal changes suggesting pancreatitis.[5,7] Both had physical signs of pancreatic inflammation.

The pertinent laboratory values are summarized in Table 1. All patients had a significantly elevated serum amylase. There were no significant differences among the three patient groups for maximum serum amylase (Fig. 1), urinary amylase, serum lipase, serum calcium, or white blood count. In contrast the amylase/creatinine clearance ratio is three times higher than normal in Groups I and III ($p < .001$) but normal in Group II. The elevated clearance ratios in Groups I and III conform well with the other objective evidence of pancreatitis. Similarly the normal clearance ratio in Group II patients is consistent with the clinical absence of pancreatitis. As shown in Fig. 2, there is very little overlap of the ranges for groups of patients with and without pancreatitis.

Discussion

Peptic ulcer disease is thought to be one of the etiologic causes of acute pancreatitis.[3] Direct penetration of an ulcer into the pancreas produces a localized inflammatory reaction in the pancreas, a phenomenon frequently observed during surgical dissection of the ulcerated duodenum. Nonetheless, we have wondered why the "pancreatitis" attributed to peptic ulcers is so often mild in comparison with the rest of the spectrum of pancreatitis seen at this institution, and have questioned whether true pancreatitis is present in these patients.

The usual criteria for making the diagnosis of pancreatitis are limited and imprecise. The characteristics of the history and physical examination may make pancreatitis difficult to distinguish from a number of other upper abdominal diseases, including common duct stones, perforated peptic ulcers, acute gastritis, and small intestinal obstruction. The laboratory test most relied upon to substantiate the diagnosis of acute pancreatitis is the serum amylase, but significant elevations occur also with liver inflammation,

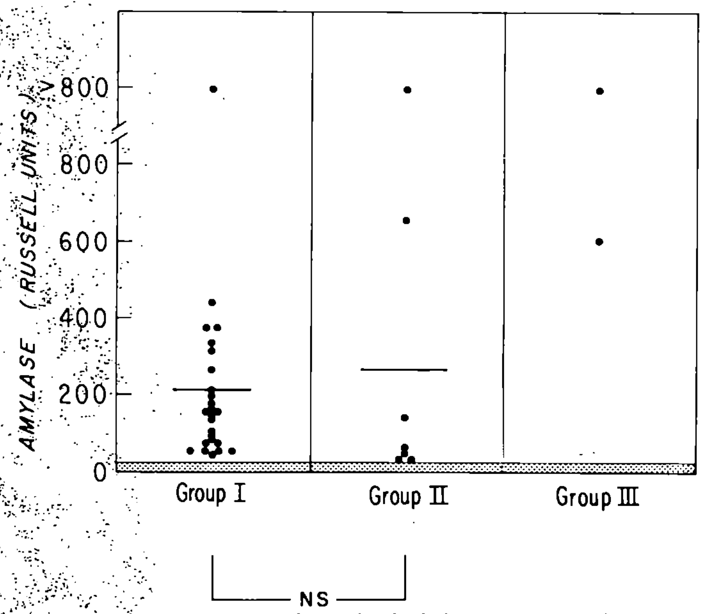

FIG. 1. Maximum Serum Amylase. The shaded area represents the normal range. The bar represents the mean for the group. There is no significant difference between the patients with pancreatitis (Group I), peptic ulcer alone (Group II) or peptic ulcer with pancreatitis (Group III).

small intestinal obstruction or infarction, uncomplicated common duct stones, and following the administration of morphine.[1,2,6,8,15] Serum lipase similarly rises in conditions other than pancreatitis.[11,13]

The amylase/creatinine clearance ratio was shown by Levitt *et al.*[12] to increase significantly above normal in acute pancreatitis. Warshaw and Fuller[14] confirmed the rise in acute pancreatitis and showed that it did not occur in other diseases associated with hyperamylasemia. In the present study we have applied this observation to patients with "acute pancreatitis" apparently caused by peptic ulcers.

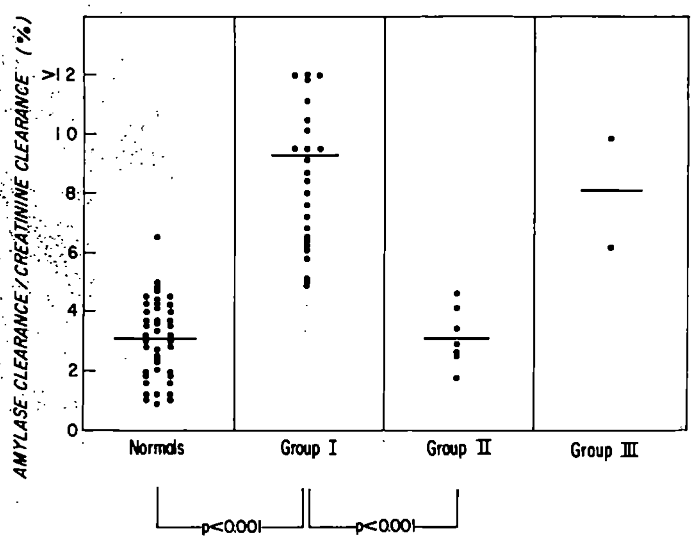

FIG. 2. Amylase clearance expressed as a percentage of creatinine clearance. Each point represents the initial value for a patient. The bar represents the mean for the group. The patients with pancreatitis (Group I) and pancreatitis with peptic ulcer (Group III) had higher values than those with peptic ulcer alone (Group II) or the normals.

The value of the amylase/creatinine clearance ratio correlated well in this study with other evidence for or against genuine pancreatitis. Thus patients with pancreatitis associated with gallstones, alcohol, or hyperlipemia had an elevated clearance ratio, as well as radiologic or surgical evidence of pancreatitis. In contrast, seven of the nine patients with peptic ulcer had a normal amylase/creatinine clearance ratio and no evidence of pancreatitis radiologically or at surgery. In only two of the nine was the clearance ratio in the pancreatitis range, and these two patients had radiologic evidence for pancreatitis as well. These findings are consistent with an occasional causal relationship between ulcers and pancreatitis, but suggest that the diagnosis of pancreatitis may be made too often in patients with ulcer disease. Although the hyperamylasemia in these patients may be secondary to a local pancreatic reaction limited to the immediate vicinity of the ulcer, or to clinically insignificant pancreatitis, it is also possible that there is abnormal absorption of amylase into the blood stream from the intestinal lumen across the defect in the mucosal barrier, the ulcer.

The importance of these observations lies in their implications for management of patients who appear to have pancreatitis. The amylase/creatinine clearance ratio is useful for confirming or questioning the diagnosis of acute pancreatitis. Patients with a normal clearance ratio should be evaluated immediately for other conditions which cause hyperamylasemia, including gastric or duodenal ulcer. Early detection of ulcer disease and exclusion of pancreatitis will facilitate more appropriate and effective treatment.

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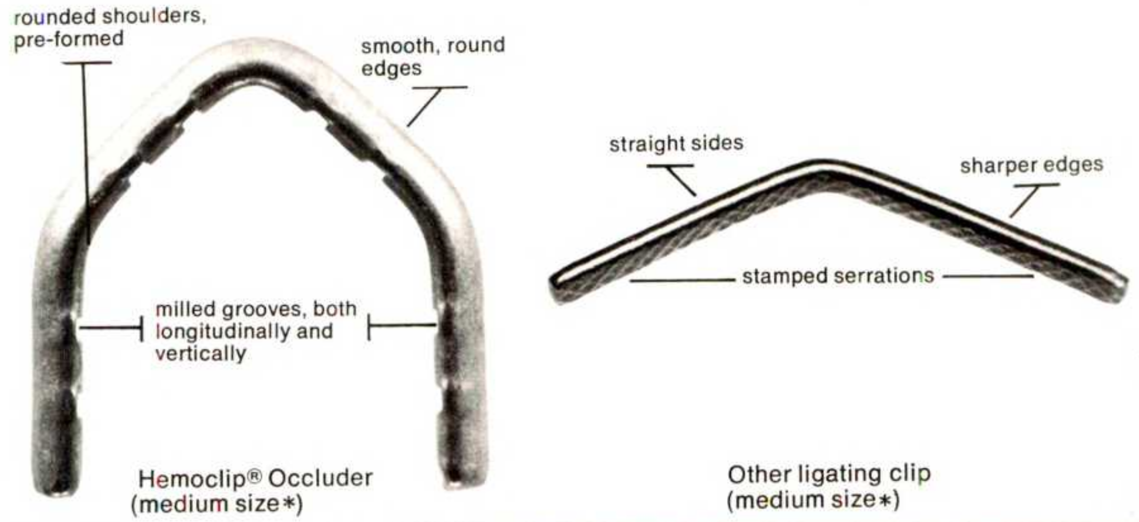
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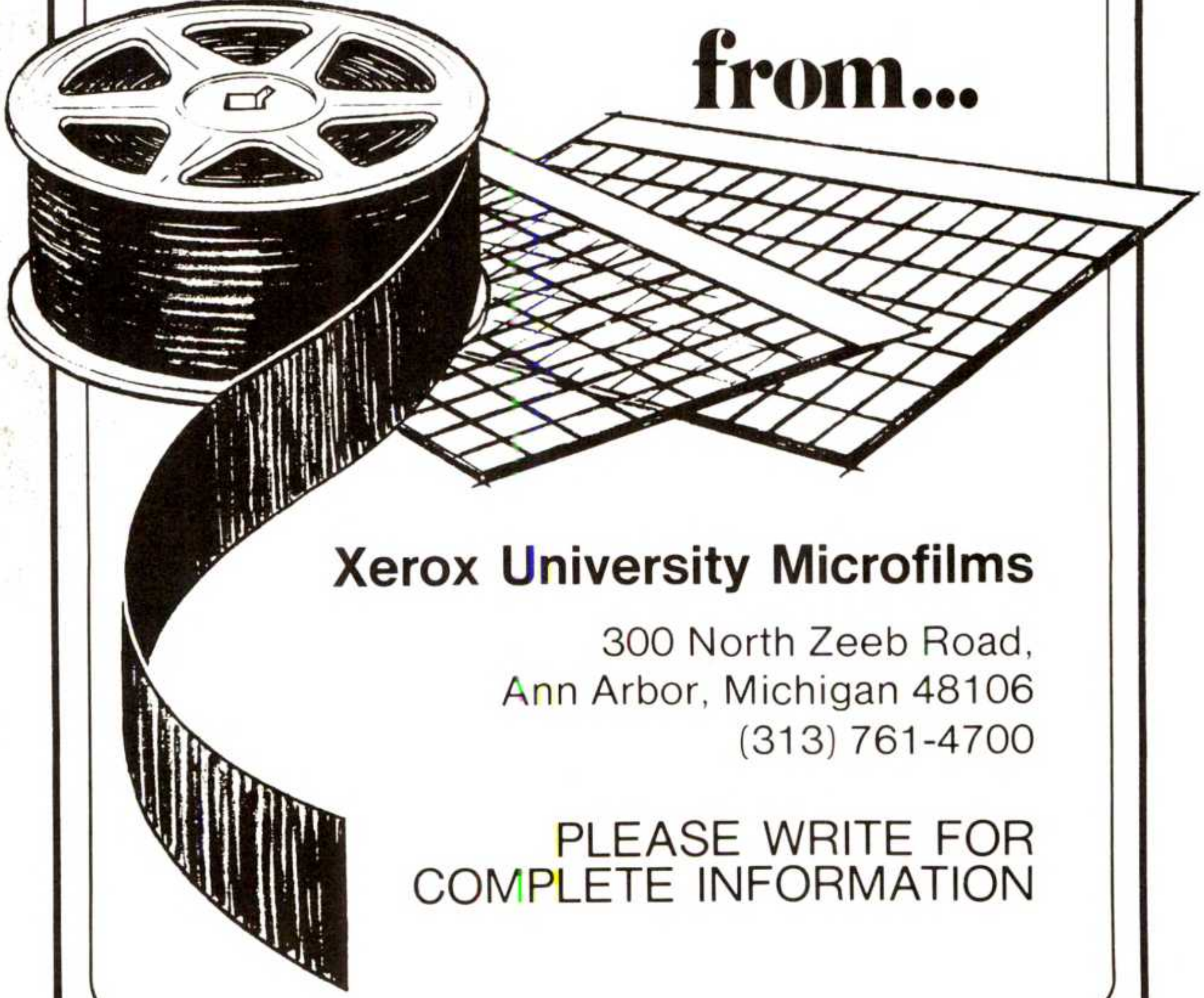

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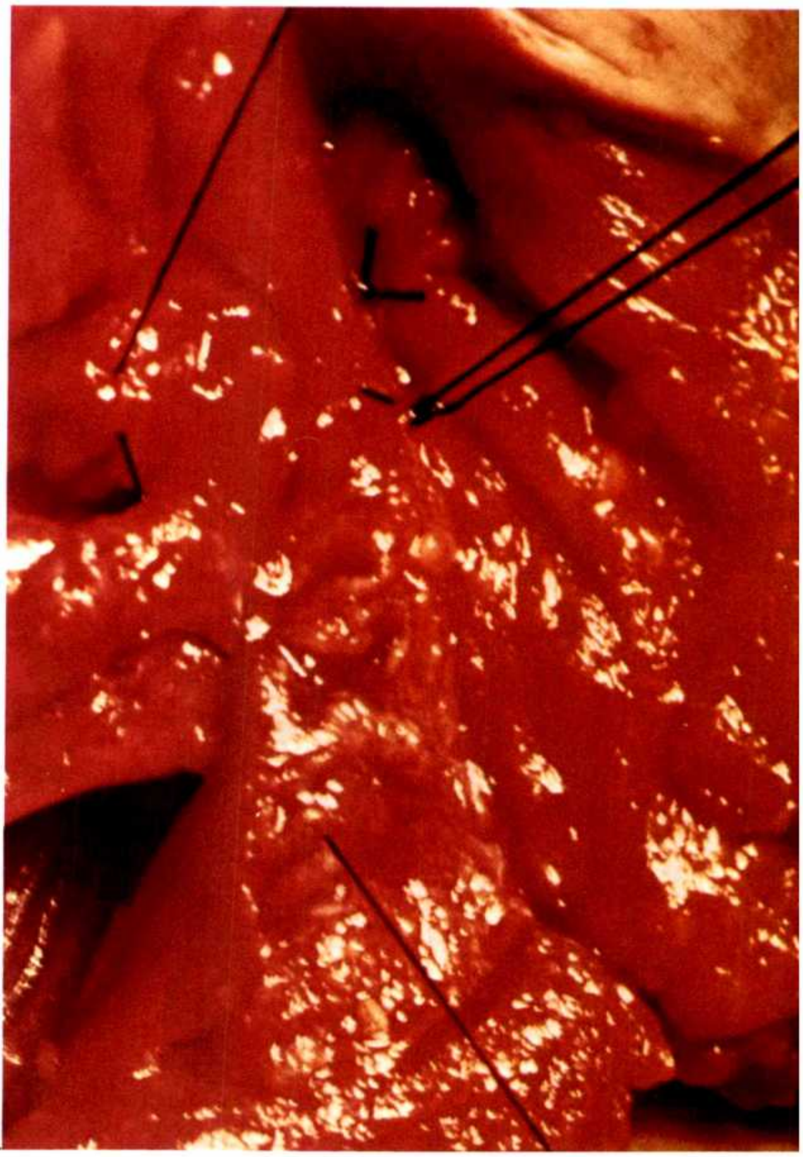

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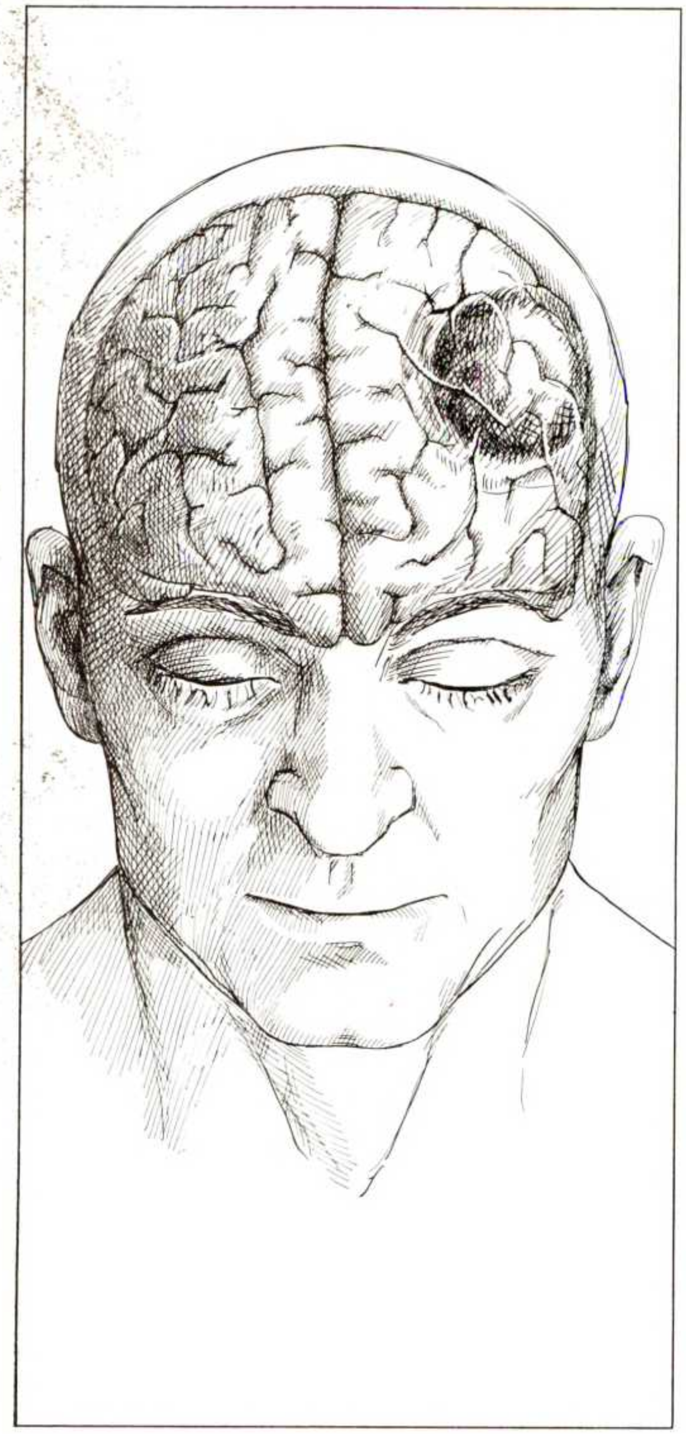
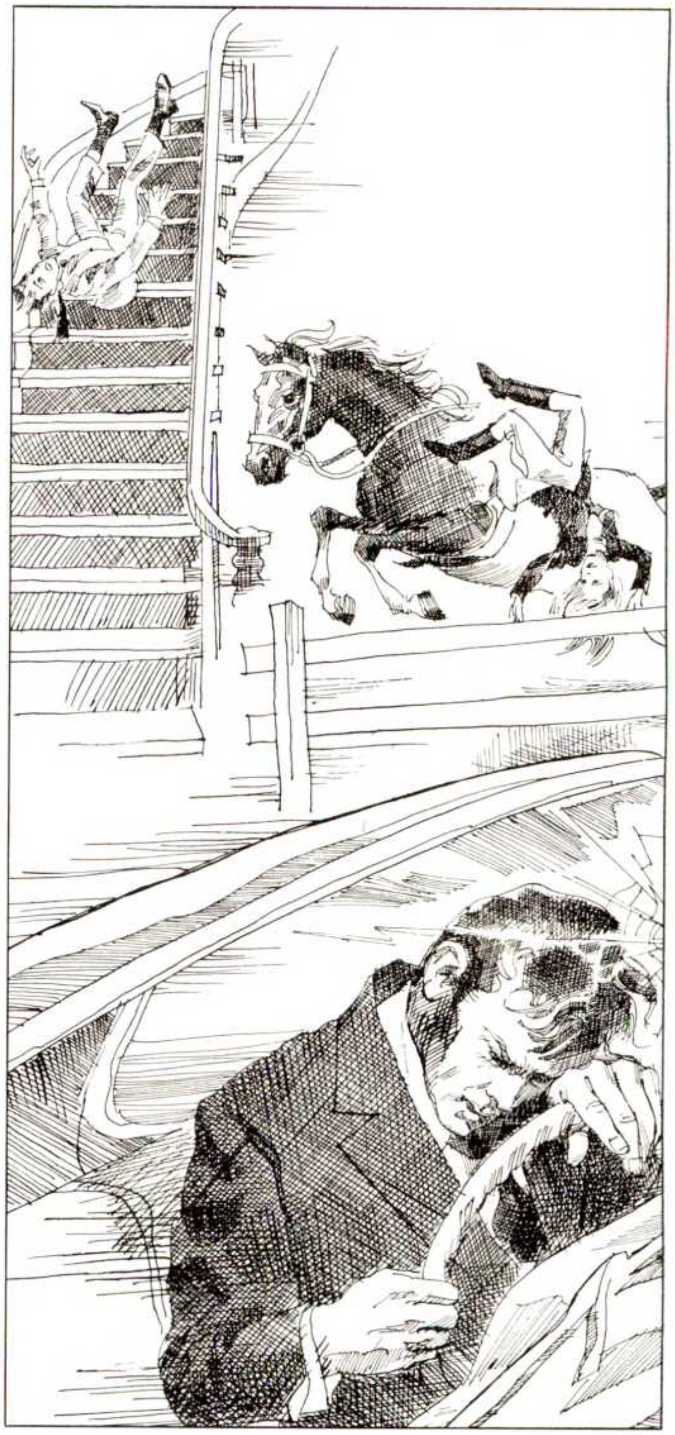


expect it in the presence of severe head injury.



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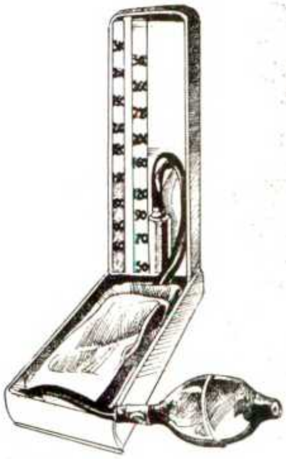

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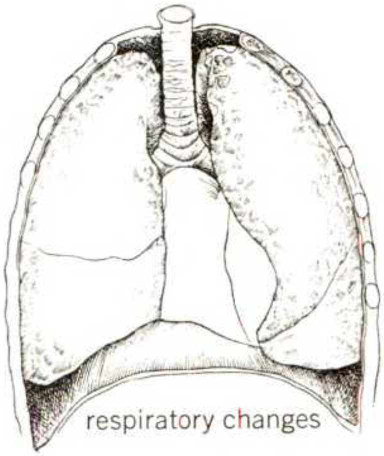

respiratory changes

dilated pupil,
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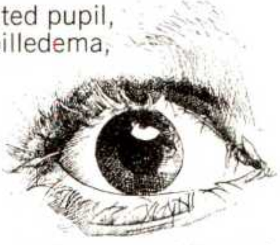
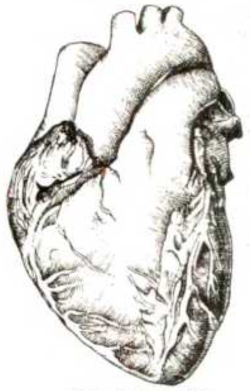


unilateral or bilateral
abducens palsy



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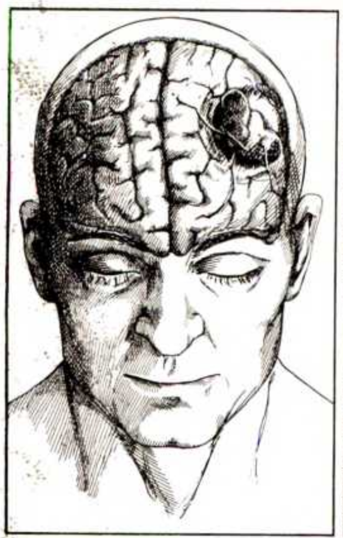

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Warnings: In patients on corticosteroid therapy subjected to unusual stress, increase dosage of rapidly acting corticosteroids before, during, and after the stressful situation. Corticosteroids may mask some signs of infection; new infections, decreased resistance, and inability to localize infection may occur. Prolonged use of corticosteroids may produce posterior subcapsular cataracts and glaucoma with possible damage to optic nerves and may enhance the establishment of secondary, fungal or viral ocular infections.

Usage in pregnancy: In pregnancy, nursing mothers, or women of childbearing potential, weigh possible benefits against potential hazards to mother and embryo or fetus. Infants of mothers on substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Elevation of blood pressure, salt and water retention, and increased excretion of potassium may occur with large doses of synthetic corticosteriods; dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion. Patients on corticosteroid therapy should not be vaccinated against smallpox and other immunization procedures should not be undertaken. Corticosteroids may suppress reactions to skin tests.

In active tuberculosis, use should be restricted to fulminating or disseminated tuberculosis and should be in conjunction with appropriate antituberculous regimen; in latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur, and patients should receive chemoprophylaxis during prolonged corticosteroid therapy.

Because rare instances of anaphylactoid reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to parenteral administration, especially in patients with history of drug allergy.

Precautions: ORAL AND PARENTERAL THERAPY—Drug-induced secondary adrenocortical insufficiency may persist for months after discontinuation of therapy and may be minimized by gradual reduction of dosage; in any situation of

stress occurring during that period, hormone therapy should be reinstituted. If patient already is receiving steroids, dosage may have to be increased. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

In hypothyroidism and in cirrhosis, there is an enhanced effect of corticosteroids. Use cautiously in patients with ocular herpes simplex for fear of corneal ulceration and perforation.

The lowest possible dose should be used, and when reduction in dosage is possible, it must be gradual. Psychic derangements may appear, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression to frank psychotic manifestations, and existing emotional instability or psychotic tendencies may be aggravated. In hypoprothrombinemia, use aspirin cautiously in conjunction with corticosteroids.

Use with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess, or other pyogenic infection; also in diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, renal insufficiency, hypertension, osteoporosis, and myasthenia gravis. Fat embolism has been reported as a possible complication of hypercortisonism. An ulcer regimen including an antacid should be considered as a prophylactic measure during prolonged therapy.

Growth and development of infants and children on prolonged therapy should be carefully followed. Motility and number of spermatozoa may be increased or decreased. Diphenylhydantoin may enhance the rate of metabolism and clearance of corticosteroids, and this may increase steroid dosage requirements.

ORAL THERAPY—Dosage must be individualized according to severity of disease and response of patient. Blood pressure, body weight, routine laboratory studies, including 2-hour postprandial blood glucose and serum potassium, and a chest x-ray should be obtained at regular intervals during prolonged therapy. Upper G.I. x-rays are desirable in patients with known or suspected peptic ulcer disease. Continued supervision of patient after cessation of corticosteroids is essential, since there may be a sudden reappearance of severe manifestations of disease for which patient was treated.

PARENTERAL THERAPY—The injectable form is sensitive to heat and should not be autoclaved when it is desirable to sterilize the exterior of the vial. Intra-articular injection may produce systemic as well as local effects. Appropriate examination of any joint fluid present is necessary to exclude a septic process. Marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis; if this complication occurs and diagnosis of sepsis is confirmed, appropriate antimicrobial therapy should be instituted. Local injection of a steroid into an infected site is to be avoided. Should not be injected into unstable joints. Patients should be impressed strongly with the importance of not overusing joints in which symptomatic benefit has been obtained as long as the inflammatory process remains active. The slower rate of absorption by intramuscular administration should be recognized.

Adverse Reactions: ORAL AND PARENTERAL THERAPY—*Fluid and Electrolyte Disturbances:* Sodium retention; fluid retention; congestive heart failure in susceptible patients; potassium loss; hypokalemic alkalosis; hypertension. *Musculoskeletal:* Muscle weakness; steroid myopathy; loss of muscle mass; osteoporosis; vertebral compression fractures; aseptic necrosis of femoral and humeral heads; pathologic fracture of long bones. *Gastrointestinal:* Peptic ulcer with possible subsequent perforation and hemorrhage; pancreatitis; abdominal distention; ulcerative esophagitis. *Dermatologic:* Impaired wound healing; thin fragile skin; petechiae and ecchymoses; erythema; increased sweating; may suppress reactions to skin tests; other cutaneous reactions. *Neurologic:* Convulsions; increased intracranial pressure with papilledema (pseudotumor cerebri) usually after treatment; vertigo; headache. *Endocrine:* Menstrual irregularities; development of cushingoid state; suppression of growth in children; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery, or illness; decreased carbohydrate tolerance; manifestations of latent diabetes mellitus; increased requirements for insulin or oral hypoglycemic agents in diabetics. *Ophthalmic:* Posterior subcapsular cataracts; increased intraocular pressure; glaucoma; exophthalmos. *Metabolic:* Negative nitrogen balance due to protein catabolism.

PARENTERAL THERAPY—Hypotensive or shock-like reaction hypersensitivity; thromboembolism; burning or tingling, especially in the perineal area (after IV injection); rare instances of blindness associated with intralesional therapy around the face and head; hyperpigmentation or hypopigmentation; subcutaneous and cutaneous atrophy; sterile abscess; postinjection flare (following intra-articular use); Charcot-like arthropathy.

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Cardiopulmonary Adjustments Following Single High Dosage Administration of Methylprednisolone in Traumatized Man

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Pharmacologic doses of methylprednisolone sodium succinate were administered to 10 critically ill patients when the steroid was the only variable. Measurements of respiratory and circulatory physiologic parameters were obtained in all patients prior to injection and at 30 and 90 minutes following injection of methylprednisolone sodium succinate. A significant increase in Cardiac Index was seen ($P<.01$) which appeared to be in association with a decrease in pulmonary vascular resistance ($P<.01$) at a time when physiologic shunting of blood through the lungs increased ($P<.01$). These changes imply improved perfusion of non- or poorly ventilated portions of the lungs. Four of ten patients demonstrated removal of lactate by the lung during the control period. Following methylprednisolone sodium succinate injection, 9 of 10 patients demonstrated production or a washout of lactate from the lungs.

GLUCOCORTICOID PREPARATIONS in pharmacologic doses have been recently advocated as primary therapy for management of both medical and surgical acutely ill patients.[2,4,7,8,15,20,26–28,31–33,43–45] Beneficial effects claimed for these preparations include stabilization of lysosomal membranes, improvement in cardiac dynamics, and a decrease in peripheral vascular resistance. Much of the available literature deals with animal models and artificially controlled systems. In most instances studies in humans have included patients who received a number of other drugs, blood, and intravenous fluids in addition to steroid preparations.[4,7,8,24,26,27] Also, many authors do not discriminate between the various glucocorticoid preparations.[27,28,34,41,44] This situation severely limits one's ability to interpret the reported data.

The present study was undertaken to investigate respiratory and circulatory effects of a high dosage of one steroid preparation, methylprednisolone sodium succinate, when administered to the acutely ill patient during a time in which the action of the steroid was the only known variable.

Method and Materials

Studies were performed on ten seriously ill patients who were admitted to the Trauma Center of the Albany Medical College. Seven patients were victims of multiple trauma accidents, one patient was in septic shock following surgery, and two patients were postoperative following repair of ruptured abdominal aneurysms. Radial artery catheters were inserted and a flow-directed triple lumen 7F Swan Ganz[55] catheter was positioned in a pulmonary artery and then advanced to a wedge position. All ten patients were intubated and ventilated with a volume cycled respirator. Pulmonary artery, pulmonary wedge and arterial blood pressures were measured by means of strain gauge transducers. Cardiac output was determined by indocyanine green dye dilution technique. Analog voltages from the densitometer and the output of selected channels of a recorder were transmitted on-line to a medium size digital computer for calculation of cardiac output, and its conversion to cardiac index based on the patient's body surface area (BSA), and for calculation of pulmonary vascular resistance determined from mean pulmonary artery pressure and pulmonary wedge pressure.[17] Mixed venous blood was obtained from the Swan Ganz catheter. Blood gases were analyzed using P_{O_2}, P_{CO_2}, and pH electrodes. Physiologic shunt fraction of blood through the lung was computed off-line using the Berggrens formula with appropriate correction for shift in the oxygen dissociation curve, hemoglobin concentration and dissolved oxygen. (Error of determination ±3%).

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TABLE 1. *Patient Description, Mean Aortic Blood, Pressure and Pulmonary Wedge Pressure in Ten Patients Receiving Methylprednisolone.*

				Mean Aortic Blood Pressure (mm Hg)			Pulmonary Wedge Pressure (mm Hg)		
Patient	Age Sex	Diagnosis	Survival or Death	Baseline	30 min	90 min	Baseline	30 min	90 min
1	14/M	Trauma	Survived	112	116	115	10	10	14
2	43/F	Trauma	Survived	97*(84)	99	90	17	8	8
3	21/M	Trauma	Survived	108	98	105	10	5	5
4	62/F	Aneurysm	Survived	135	112	114	3	4	3
5	39/M	Trauma	Survived	102	96	107	13	13	13
6	37/M	Septic Shock	Survived	74	72	72	—	—	—
7	19/F	Trauma	Survived	100*(62)	86	75	9	11	14
8	29/M	Trauma	Died	102	105	108	18	20	20
9	81/M	Trauma	Died	88*(48)	84	71	6	6	6
10	69/M	Aneurysm	Died	63*(96)	54	50	10	10	8
Mean				98.1	92.2	90.7	10.7	9.7	10.1
S.E.				±6.3	±6.0	±7.1	±1.6	±1.6	±1.8
					P<.05	P-NS		P-NS	P-NS

*Change in mean aortic pressure immediately following injection of methylprednisolone sodium succinate.

Oxygen consumption was determined by the Fick equation from cardiac output multiplied by the arterial-venous oxygen content difference [[.0031 (P_{aO_2}) + Hb (1.39) (arterial saturation)] - [.0031 (P_{vO_2} Hb (1.30) (venous saturation)]]. Oxygen delivery was obtained by multiplying cardiac output by arterial oxygen content. (Error of determination ±21 ml/min).

Limb blood flow, an indication of peripheral perfusion, was obtained by the method of English *et al.*[9] using an impedance plethysmograph. The impedance of a segment of the lower extremity provides a measure of total limb volume.[5,6,23] The change in volume after sudden venous occlusion by a rapid-inflating thigh pressure cuff is proportional to blood flow.

Limb vascular resistance was determined by dividing mean aortic pressure by limb blood flow. Peripheral vascular resistance was determined by dividing mean aortic pressure by cardiac output.

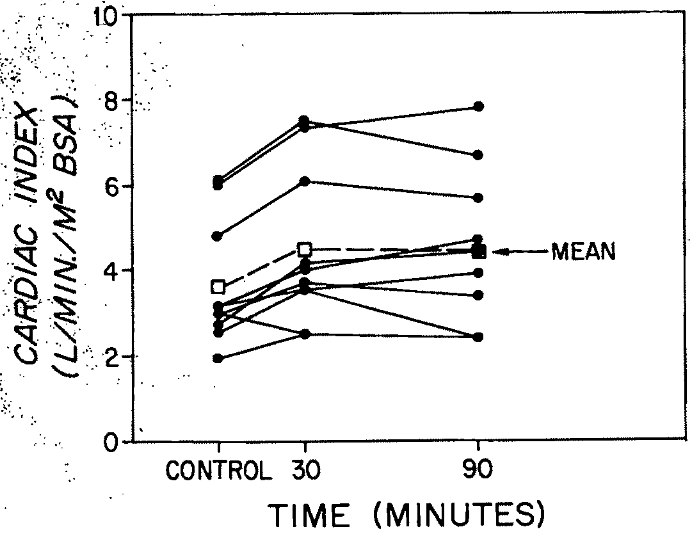

FIG. 1. Cardiac Index in L/min/m² BSA at baseline, 30 and 90 minutes after injection of methylprednisolone sodium succinate. The increase after injection was significant.

Lactate levels were determined by enzymatic reaction using a glycine buffer, lactic dehydrogenase suspension and 8% perchloric acid and spectrometer determination.*

Control measurements were made of arterial, pulmonary artery and pulmonary wedge pressures, hemoglobin concentration, cardiac index and limb blood flow. Both arterial and mixed venous bloods were analyzed for pH, P_{O_2}, and P_{CO_2} and lactate concentrations. From the time of baseline measurements and for the next ninety minutes no blood nor medications were administered. No alterations were made in the respirator settings. Following completion of the collection of the control samples, methylprednisolone sodium succinate† (30 mg/kg of body weight) was injected as a bolus into the proximal lumen of the Swan Ganz catheter. Thirty and 90 minutes after injection all of the above measurements were repeated. In four patients arterial blood pressure was recorded continuously for the entire ninety minutes.

Informed consent for the above procedures was obtained from the patient's legal guardian after the nature, purpose and risks of all procedures to be performed were explained according to the recommendations in the Declaration of Helsinki.

All statistics employ Student's T test for paired variance unless otherwise stated. All comparisons are referenced to baseline values.

Results

The ten patients studied included seven males and three females with ages ranging 19–81 years (Table 1). Eight of the ten patients developed the adult respiratory distress syndrome as evidenced by characteristic chest X-Ray changes and elevated levels of pulmonary physiologic shunting at some time early in their hospital course.

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*Sigma Chemical Company, No. 826-UV, St. Louis, Missouri.
†Upjohn, Kalamazoo, Michigan.

TABLE 2. *Cardiac Dynamics, Physiologic Shunt Through Lungs, Oxygen Delivery and Oxygen Consumption in Ten Patients Receiving Methylprednisolone.*

	Cardiac Index (L/min/m² BSA)			Pulse Rate (beats/min)			Physiologic Shunt %			Oxygen Delivery (ml/min)			Oxygen Consumption (ml/min/m² BSA)		
Patient	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min
1	6.0	7.5	6.7	144	132	132	7.1	21	18	1948	2301	2023	202	192	185
2	3.2	4.0	4.7	90	90	96	10	12	18	774	941	1073	122	151	147
3	4.8	6.1	5.7	114	108	108	13	16	17	1327	1607	1499	168	157	154
4	2.7	4.2	4.4	102	102	108	12	22	21	682	1048	1074	120	152	179
5	2.6	3.6	2.5	60	63	60	10	24	20	722	889	686	85	96	86
6	3.2	3.6	3.9	102	96	90	14	21	21	924	989	1096	166	156	164
7	6.0	7.4	7.8	108	120	108	15	14	13	887	1057	1133	149	129	168
8	2.5	2.6	2.5	96	96	96	18	20	25	637	636	627	110	110	91
9	2.0	2.6	2.5	69	67	66	32	39	36	594	772	699	85	95	105
10	3.0	3.7	3.4	84	84	84	43	48	45	752	905	832	119	131	132
Mean	3.6	4.5	4.4	97	96	95	17.4	23.7	23.4	925	1114	1074	133	137	141
S.E.	±0.5	±0.6	±0.6	±7.5	±6.8	±6.7	±3.6	±3.6	±3.1	±131	±154	±135	±12	±9.7	±11
		P<.001	P<.01		P-NS	P-NS		P<.01	P<.01		P<.01	P<.01		P-NS	P-NS

Cardiac Index

The average presteroid cardiac index was 3.6± 0.5 l/min/m² BSA (Table 2, Fig. 1). Thirty minutes after the administration of methylprednisolone sodium succinate the cardiac index increased in all ten patients to an average of 4.5± 0.6 l/min/m² BSA ($P < .001$). At 90 minutes the cardiac index was still elevated over baseline values in eight of the ten patients. The mean cardiac index at ninety minutes was 4.4± 0.6 l/min/m² BSA ($P < .01$). Thus, the rise in the cardiac index associated with the injection of methylprednisolone sodium succinate was significant.

Pressure Measurements and Pulse Rate

Pulmonary wedge pressure, a reflection of left atrial pressure, remained within 2 mm Hg of control over the ninety minute study period in five of the nine patients in whom it was measured (Table 1). Changes that did occur in the mean pulmonary wedge pressure were not statistically significant. In both patients in whom wedge pressure rose, the cardiac index was higher than baseline values. However, in two patients in whom the wedge pressure fell, the cardiac index did not fall, but rose also.

Average mean radial artery pressure was initially 98 ± 6.3 mm Hg (Table 1). Thirty minutes after methylprednisolone sodium succinate, it fell to a mean of 92.2± 6.0 mm Hg ($P < .05$). Although at ninety minutes the mean was 90.7± 7.1 mm Hg, this was not significantly below control because of the wide variability between patients.

Among four patients in whom arterial pressure was continuously recorded following methylprednisolone sodium succinate administration, an abrupt drop in blood pressure occurred in three patients from a mean of 95 mm Hg to a mean of 64.6 mm Hg within four minutes of the injection (Table 1). The period of hypotension was brief and all values approached baseline by thirty minutes after injection. The hypotension was not treated with any additional medication or intravenous fluid administration.

There was no significant change in pulse rate following injection (Table 2).

Hemoglobin Concentration and Arterial Blood Gases

Hemoglobin levels did not change during the period of study (Table 3). Inspired oxygen concentrations for the ten patients ranged from 20% to 80%. Five patients received positive end-expiratory pressure ventilation which was not changed throughout the period of study. The range of end-expiratory pressure was 5 cm H_2O to 20 cm H_2O. Mean arterial pH remained virtually constant. Arterial P_{O_2} decreased in nine of ten patients after injection of methylprednisolone sodium succinate. The drop to a mean arterial P_{O_2} of 91 ± 9 mm Hg at ninety minutes was significant (P <

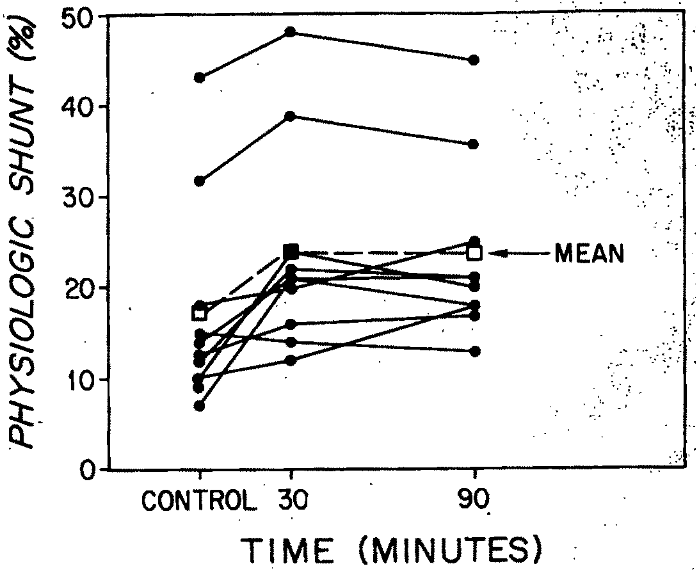

FIG. 2. Physiologic shunt through the lung at baseline, 30 and 90 minutes after injection of methylprednisolone sodium succinate. The increase after injection was significant.

TABLE 3. *Blood Gases, Inspired Oxygen Concentration and Hemoglobin in Ten Patients Receiving Methylprednisolone*

	Systemic Arterial Blood Gases												
	Baseline			30 Min			90 Min				Hemoglobin gm %		
Patient	pH	Po_2 mm Hg	Pco_2 mm Hg	pH	Po_2 mm Hg	Pco_2 mm Hg	pH	Po_2 mm Hg	Pco_2 mm Hg	Inspired Oxygen Fraction	Baseline	30 Min	90 Min
1	7.40	110	32.6	7.40	127	42.6	7.41	132	42.1	.40	11.3	10.5	10.2
2	7.41	125	35.4	7.41	109	33.9	7.38	94	43.0	.30	10.1	9.8	9.7
3	7.42	91	32.4	7.40	92	36.6	7.41	89	31.1	.20	10.7	10.3	10.4
4	7.50	123	34.0	7.51	84	32.1	7.46	82	31.8	.40	11.3	11 3	11.3
5	7.52	161	31 5	7.50	91	33.8	7.46	96	34.8	.40	10.5	9.6	10.5
6	7.41	118	28.7	7.41	94	29 .	7.43	95	34.1	.50	10.2	10.2	10.2
7	7.36	122	37.4	7.42	120	35.1	7.38	126	37.5	.40	10.6	10.2	10.5
8	7.49	110	31.8	7.49	94	29.9	7.49	78	36.7	.50	9.2	9.1	9.3
9	7.53	87	34 7	7.47	69	38.3	7.47	67	34.4	.80	11.0	11.8	11 5
10	7.44	54	34 6	7.41	52	36.8	7.44	51	35.7	.70	10.8	10.9	10.7
Mean	7.45	110	33.3	7.44	93.2	34.8	7.43	91.0	36.1		10.6	10.4	10.4
S.E.	±.02	±9.0	±.8	±.01	±7.1	±1.3	±.01	±7.7	±1.2		±.2	±.2	±.2
				P -NS	P<.05	P<.05	P -NS	P .05	P<.05			P -NS	P -NS

.05). Despite fixed respirator settings, arterial Pco_2 increased significantly from 33.3± 0.8 mm Hg to 36.1± 1.2 mm Hg at ninety minutes (P <.05).

Oxygen Delivery, Oxygen Consumption and Physiologic Shunt

Oxygen delivery increased in nine of ten patients following methylprednisolone sodium succinate injection (Table 2). Baseline oxygen delivery averaged 925± 131 ml/min. The mean at 30 minutes after injection had increased to 1,114± 154 ml/min (P<.01), and after 90 minutes the mean was 1,074± 135 ml/min (P<.01). Thus, the rise in oxygen delivery after steroid injection was statistically significant.

Control oxygen consumption averaged 133± 12 ml/min/m^{2}BSA. Thirty minutes after methylprednisolone sodium succinate injection oxygen consumption was virtually unchanged from presteroid levels. No significant change was seen ninety minutes after injection (Table 2).

Baseline physiologic shunt of blood through the lung averaged 17.4± 3.6% (Table 2, Fig. 2). Thirty minutes after methylprednisolone sodium succinate physiologic shunt increased in nine of ten patients to an average of 23.7± 3.6% (P<.01). At 90 minutes the shunt remained significantly elevated over baseline at a mean of 23.4± 3.1% (P<.01). While physiologic shunt of blood through the lungs and cardiac index both increased significantly following the administration of methylprednisolone sodium succinate, the correlation between the two parameters was not significant (r= .28; P> .05 : Spearman rank correlation coefficient).

Pulmonary Vascular Resistance

Control pulmonary vascular resistance averaged 180 ±25 dyne-sec/cm^5 (Table 4) (Normal 120 dyne-sec/cm^5).

TABLE 4. *Pulmonary, Limb and Peripheral Vascular Resistances in Ten Patients Receiving Methylprednisolone*

	Pulmonary Vascular Resistance (dyne-sec/cm^5)			Limb Flow (ml/min/gm)			Limb Vascular Resistance (dyne-sec/cm^5)			Peripheral Vascular Resistance (dyne-sec/cm^5)		
Patient	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min	Baseline	30 Min	90 Min
1	116	67	63	4.44	2.62	3.68	.238	.419	.298	1499	1242	1378
2	250	152	160	2.61	3.39	2.45	.575	.432	.534	2434	1987	1538
3	62	62	46	5.05	2.90	2.36	.332	.509	.607	1807	1290	1479
4	262	143	150	2.50	1.71	1.41	.700	.845	1.050	4015	2141	2080
5	84	84	—	2.75	4.01	2.92	.470	.306	.467	3150	2141	3437
6	125	137	134	2.84	3.35	3.74	2.160	1.780	1.600	1857	1606	1482
7	215	185	144	0.52	0.86	0.93	2.370	1.25	1.000	1338	933	772
8	195	144	211	3.35	2.55	3.90	.470	.622	.427	3276	3243	3469
9	287	241	236	1.12	0.63	1.07	1.140	1.743	.982	3533	2594	2281
10	202	154	165	1.63	1.75	1.90	.523	.467	.346	1686	1172	1181
Mean	180	137	145	2.68	2.38	2.44	.897	.832	.737	2460	1835	1910
S.E.	±25	±17	±20	±0.40	±0.40	±0.40	±.240	± 178	± 130	±303	±229	±290
		P<.01	P<.05		P -NS	P -NS		P -NS	P -NS		P<.01	P<.05

TABLE 5. *Lactate Concentrations and Arterial-Pulmonary Artery Lactate Differences in Ten Patients Receiving Methylprednisolone*

Patient	Arterial Lactate (mg %) Baseline	30 Min	90 Min	Pulmonary Artery Lactate (mg %) Baseline	30 Min	90 Min	Arterial-Pulmonary Artery Lactate Difference (mg %) Baseline	30 Min	90 Min
1	11.2	16.1	15.3	10.8	12.8	9.20	0.4	3.3	6.1
2	26.2	4.5	19.9	18.7	1.8	13.2	7.5	2.7	6.7
3	16.5	22.3	16.8	17.4	18.8	13.9	−0.9	3.5	2.9
4	1.5	10.7	20.5	3.9	10.0	12.8	−2.4	0.7	7.7
5	18.0	24.2	10.9	23.0	18.1	9.4	−5.0	6.1	1.5
6	27.9	25.0	12.1	31.2	22.7	12.8	−3.3	2.3	−0.7
7	11.7	16.4	18.0	8.7	10.3	13.3	3.0	6.1	4.7
8	37.3	36.9	34.5	29.8	37.3	29.9	7.5	−0.4	4.6
9	20.6	10.6	24.7	14.7	8.2	17.4	5.9	2.4	7.3
10	35.0	18.4	33.6	34.1	15.7	28.2	0.9	2.7	5.4
Mean	20.6	18.5	20.6	19.2	15.6	16.0	1.9	2.9	4.6
S.E.	±3.5	±2.9	±2.6	±3.2	±3.1	±2.3	±1.4	±0.6	±0.8
		P-NS	P-NS		P-NS	P-NS		P<.001	P<.001

Thirty minutes after injection of methylprednisolone sodium succinate the pulmonary vascular resistance had decreased markedly from control levels to a mean of 137± 17 dyne-sec/cm^5 (P<.01). At the end of ninety minutes the pulmonary vascular resistance was decreased in seven of the nine patients in whom it was determined, yielding a mean of 145± 20 dyne-sec/cm^5 (P<.05).

Peripheral Vascular Resistance, Limb Blood Flow and Limb Vascular Resistance

Peripheral vascular resistance decreased significantly following the administration of methylprednisolone sodium succinate, falling from a mean control value of 2,460± 303 dyne-sec/cm^5 to 1,835± 229 dyne-sec/cm^5 following the injection (P<.01). It remained less than control at ninety minutes after injection for a mean of 1,910± 290 dyne-sec/cm^5 (P<.05) (Table 4).

Despite this significant decrease in peripheral vascular resistance the limb vascular resistance and limb blood flow did not change significantly at either thirty or at ninety minutes following injection (Table 4). In five of ten patients in whom limb vascular resistance did increase, the cardiac index was concomitantly increasing rather than decreasing.

Lactate Concentrations

Control arterial lactate levels averaged 20.6± 3.5 mg% (Table 5). Control pulmonary artery lactate averaged 19.2 ±3.2 mg%. In six patients arterial lactate exceeded pulmonary artery lactate by an average of 4.2 mg%. This positive arteriovenous difference in lactate concentrations during steady state conditions is an indication of production or washout of lactate from the lungs. However, in four patients the arteriovenous difference was negative by an average 2.9 mg% indicating possible uptake of lactate by the lung. This phenomenon of apparent lactate storage or consumption by the lung has not been previously reported in man, although a negative arteriovenous difference has been observed in dogs.[11] Thirty minutes following methylprednisolone sodium succinate injection the average systemic arterial lactate was 18.5 ±2.9 mg%, whereas the average pulmonary artery lactate was 15.6 ±3.1 mg%. In nine of ten patients at thirty minutes after injection the arteriovenous difference was positive an average of 2.9 ±0.6 mg% indicating that almost all patients were now washing out lactate from their lungs or their lungs were producing lactate. All patients with negative control arteriovenous differences became positive. By 90 minutes the apparent lactate washout or production had increased over baseline values even further for a mean arteriovenous difference of 4.6± 0.8 mg% (P<.001).

Survival

Seven patients survived and three patients died (Table 1). Only the physiologic shunt of blood through the lung and arterial lactate levels appeared to be of statistically significant value in predicting survival (P<.05). Physiologic shunts were highest in the three patients who died. They had an average presteroid shunt of 31% (range 18 - 43). Average baseline shunts of the survivors were 11.6% (range 7.1 - 15%). After methylprednisolone sodium succinate the shunts of most of the patients increased, including those of survivors as well as those who died.

The average presteroid arterial lactate concentrations for the patients who died was 31 mg% (range 20.6 - 37.3 mg%) and in the survivors the average was 16 mg% (range 1.5 - 27.9 mg%). In only one survivor was the lactate level greater than 20 mg% on more than one occasion whereas, among those who died, all three patients had lactate levels greater than 20 mg% at least twice during the study. Improvement in the cardiac index was not followed by a decrease in the blood lactate level up to ninety minutes after the injection of methylprednisolone sodium succinate.

Discussion

Significant effects of methylprednisolone observed in this group of patients included an increase in cardiac output and a fall in peripheral vascular resistance. In addition, there was a fall in pulmonary vascular resistance associated with an increased pulmonary physiologic shunt and a fall in arterial P_{O_2}.

The increased cardiac output observed in all of our patients thirty minutes after injection of steroid is consistent with the findings of a number of other investigators.[7,8,27,28,43,44] Wilson and Fisher,[44] who followed a test sequence comparable to that of the present study, found a 23% increase in cardiac output of 23 patients at 30 minutes after injection and a 19% increase at 60 minutes after injection of either hydrocortisone, methylprednisolone, or dexamethasone. However, at 90 minutes their patients' average cardiac output was lower than control. In the present study, cardiac output was lower than control in only one of ten patients at 90 minutes. The overall increase in cardiac output cannot be ascribed to an increased filling pressure of the left ventricle or an increased pulse rate, for neither pulmonary wedge pressure nor pulse rate changed significantly.[27] It is possible that methylprednisolone has a positive inotropic effect on the myocardium, although experimental support for such a hypothesis remains controversial.[13,32]

The increase in cardiac output led to an increase in oxygen delivery, but body metabolism did not change in response to the rise in delivery of oxygen since there was no increase in oxygen consumption. This is in contrast to the direct relationship found between oxygen consumption and oxygen delivery in patients receiving positive end-expiratory pressure ventilation.[22]

The above increase in cardiac output appears to be associated with increased perfusion of blood to areas other than peripheral skeletal musculature, for total peripheral resistance of these patients decreased significantly while limb vascular resistance remained unchanged. There is previous evidence that increased flow through the renal vasculature may occur following steroid administration.[34] The decreases in peripheral vascular resistance in the present study are consistent with those reported by other investigators both in experimental animals and in man.[7,8,27,28,43] However, our results differ from those of Wilson and Fisher[44] in that, following an initial decrease in peripheral vascular resistance in patients in septic or cardiogenic shock, they calculated an overall increase, rather than a sustained decrease, in peripheral vascular resistance at 90 minutes.

Resistance to blood flow through the pulmonary bed also decreased strikingly. At the same time, physiologic shunt of blood through the lungs increased. It would appear that methylprednisolone sodium succinate caused a redistribution of pulmonary blood flow by increasing perfusion to non or poorly ventilated portions of the lung. This redistribution is analogous to that found in the dog during unilateral atelectasis or hypoxia in association with systemic hypoxemia.[16,19] Thus, this drug appears to override the normal mechanism for controlling ventilation-perfusion ratios in poorly ventilated portions of the lung. The resistance changes in our patients are consistent with the drop in pulmonary vascular resistance observed by Rosenbaum *et al.*[27] in septic shock patients treated with steroids, but are not consistent with the rise in pulmonary vascular resistance they observed in cardiogenic shock patients treated with steroids.

There was a sudden drop in blood pressure in three of the four patients in whom continuous recordings were made during the injection of methylprednisolone sodium succinate. This phenomenon has been observed previously immediately after injection of steroids in both humans and dogs.[36,44] Thomas and Brockman[36] found an abrupt fall in cardiac output associated with a drop in blood pressure both of which returned to baseline within ten minutes in eight of ten dogs. Their study indicates a possible hazard of administering very large dosages of corticosteroids in that in the remaining two dogs there was no recovery from the circulatory depression following steroid injection and death resulted within 15 minutes. In all three of our patients by 30 minutes the blood pressure approached control values. However, mean blood pressure of the patients in this study remained significantly decreased at 30 minutes following injection of methylprednisolone sodium succinate. This is in contrast to the findings of several other investigators who report no significant change in blood pressure after steroid injection.[7,26,28,34]

Lactate is the final product of the metabolism of glucose in an anerobic environment. Lactate can be converted to pyruvate only in the presence of molecular oxygen in order to maintain a normal DPNH + H: DPN ratio.[3]

$$\text{Pyruvate} + \text{DPNH} + \text{H} \quad \overset{\text{lactic dehydrogenase}}{\rightleftarrows} \quad \text{Lactate} + \text{DPN}$$

Pyruvate may then enter into the Kreb's cycle to potentiate the breakdown of glucose into water, carbon dioxide, and energy. Net production of lactate by an organ has been interpreted to represent anerobic metabolism during periods of cellular hypoxia.

Within the literature there appears to be a controversy concerning the ability of pulmonary tissue to produce lactate. On the one hand there is evidence that during hypoxia "excess lactate" is produced which corresponds closely to the magnitude of the hypoxia.[14] Several investigators report positive arteriovenous differences in lactate concentrations across the pulmonary bed in patients with severe pulmonary disease and suggest that the lungs were adding lactate to the arterial blood.[25,33] By following glucose metabolism it has been found that approximately 30% of this sugar was converted into lactic acid within the lung.[10,40,46] On the other hand some investigators could find no difference in lactate concentrations across the lung bed.[12,18] The present opinion is that lactate is probably produced by the lung and that this production may even occur in states other than those of hypoxia.[38,39] Furthermore, it is also believed that the lungs do not have appropriate enzymes to allow utilization of lactate.[37] Lactate levels have been found to be elevated in periods of systemic shock, being somewhat higher in hemorrhagic shock than in septic shock.[1] Steroids are reported to decrease systemic lactic acid levels several days after injection.[7,8,27,29–31] The steroids appear to have a gluconeogenic effect.[21] This decrease of lactate toward normal levels has been attributed to an initial rise associated with a washout of lactate from previously poorly perfused organs, followed by a fall as lactate production diminishes. In contrast, in this present study there was no significant reduction in lactate levels. However, there appeared to be a marked redistribution of lactate when arteriovenous differences were determined. Previously unreported in man is the finding that in at least three patients there were differences between pulmonary artery lactate and systemic arterial lactate where the former were the higher of the two values. This would indicate that as blood crossed the pulmonary vascular bed some lactate entered the lung. After methylprednisolone sodium succinate, lactate levels of all arterial samples equalled or exceeded those of pulmonary artery samples, indicating that in response to treatment, either a washout or a production of lactate from the lung occurred. A washout from the lung might occur with a redistribution of blood flow to the lung in association with the observed increase in shunt and decrease in pulmonary vascular resistance. The increase in physiologic shunting of blood through the lung, an apparently undesirable effect in patients already suffering from compromised ventilation may, in conjunction with the decrease in pulmonary vascular resistance, indicate improved perfusion of non- or poorly ventilated portions of the lung and be beneficial in the long term treatment of their adult respiratory distress syndrome.

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Occult Adrenal Insufficiency in Surgical Patients

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Eight patients admitted to a University hospital with acute surgical problems and related adrenal insufficiency were reviewed and three are presented in detail. Surgical stress and continued sepsis played major roles in the lack of responsiveness to usual modes of therapy until the adrenal insufficiency was corrected. The patients fell into three major clinical categories of adrenal insufficiency. Chronic illness and sepsis are shown to affect steriod production and metabolism, as well as adrenal responsiveness to ACTH. Pharmacologic amounts of steroids are often needed in patients with shock, gram negative sepsis and prolonged illnesses, even if normal or elevated serum cortisols are present. Therapeutic trials of cortisol administration are shown to be confusing when not accompanied by easily performed diagnostic tests of adrenal function. It is emphasized that a pretreatment serum cortisol should be obtained whenever possible. The evaluation of adrenal function is of lifelong importance to the patient.

THE SURGEON is often faced with acute situations wherein his patient exhibits nonresponsiveness to the usual therapeutic maneuvers. Under these circumstances, attention is usually focused on hypovolemic states, the myocardium, respiratory tract, sepsis, and pulmonary or fat embolism. Unrecognized adrenal insufficiency should be included in the differential diagnosis.

Acute adrenal insufficiency is seen in three major clinical situations:

I. In the first group are patients with unrecognized Addison's disease in whom a crisis has been precipitated by trauma, a surgical procedure, intercurrent infection or inadvertent discontinuation of corticosteroid therapy.

II. In the second group are those patients with iatrogenic adrenal insufficiency in whom long-term adrenocortical steroid therapy has been discontinued for one reason or another, and in whom acute stress may precipitate adrenal insufficiency. The number of patients in this category is rising rapidly as disease complexes responding to steroid therapy increase.

III. In the third group are patients admitted to an emergency unit or to the hospital in extremis, or hypotensive from unknown causes, in whom adrenal failure may possibly play a role. It is in this latter group of patients in whom pharmacologic doses of glucocorticoid therapy may be indicated as one form of nonspecific therapy. This might include patients with severe gram-negative infections, the Waterhouse-Friderichsen syndrome, postmyocardial infarction patients on anticoagulants, patients with metastatic carcinoma to the adrenals, and pseudotumor cerebri.

The adrenal secretory responses to continued infection, chronic illness and stress are poorly understood. Depression of adrenal secretion and diminished responsiveness to ACTH often develop during severe or prolonged infection.

This report is concerned with eight patients (Table 1) admitted to the surgical service at University Hospitals of Cleveland presenting acute problems and related adrenal insufficiency during their hospital course. Surgical stress and continued sepsis played strategic roles in the lack of responsiveness to therapy in some of these patients until the adrenal insufficiency was corrected.

Three examples of patients with adrenal insufficiency are summarized to emphasize the problems encountered in their surgical care and convalescence.

Case Reports

G.S. #235-103. A 53-year-old female was admitted to the Medical Service of University Hospitals January 21, 1968 with weakness and vomiting of one month's duration. Chills and fever had been present for three weeks. She continued to have anorexia, vomited frequently, and had lost 16 pounds. There was no change in bowel habits, jaundice or symptoms of peptic ulcer.

Past history was noncontributory except for congenital toxoplasmosis of the eyes.

Physical examination: T. 36.5C; P. 80/min; R 20/min; B.P. 110/70 mm Hg.

Examination revealed a slender woman in no acute distress. Abdomen

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TABLE 1. *Summary of Patients with Nonresponsive Clinical Problems Associated with Hypoadrenalism*

Patient	Age	Sex	Presenting Clinical Problems	Surgical Diagnosis	Category Of Hypoadrenalism
G.S.	53	F	Hypotension, Fever, Vomiting	Cholelithiasis	I
M.B.	71	F	Sepsis, Toxic Delirium, Fever	Perforated Sigmoid Diverticulitis	I
B.A.	57	F	Hypotension, Fever	Agnogenic Myeloid Metaplasia Splenectomy	II
D.F.	79	M	Vomiting, Distension, Diarrhea, Lethargy, Sepsis	Rheumatoid Arthritis Sigmoid Vesical Fistula Colostomy	II
M.E.B.	58	F	Hypotension, Fever, Lethargy, Apnea	Rheumatoid Arthritis Necrosis of Hip	II
R.Y.	45	F	Hypotension, Sepsis, Fever	Laparotomy Gram Negative Sepsis	III
W.B.	57	M	Weakness, Vomiting, Weight Loss	Metastatic Carcinoma of Prostate	III
C.P.	17	M	Chronic Illness, Sepsis, Fever	Portal Vein Hypertension Meso-caval Shunt	III

showed minimal tenderness in the epigastrium and to the right of the umbilicus. Bowel sounds were normal. No masses palpated. Laboratory findings were normal. Urinalysis negative.

X-ray examination of the chest showed no significant pulmonary pathology. Electrocardiography on admission showed ST-T-U changes across the anterior precordium, consistent with electrolyte imbalance. The gallbladder demonstrated numerous small nonopaque calculi. Gastrointestinal x-rays showed a small hiatus hernia.

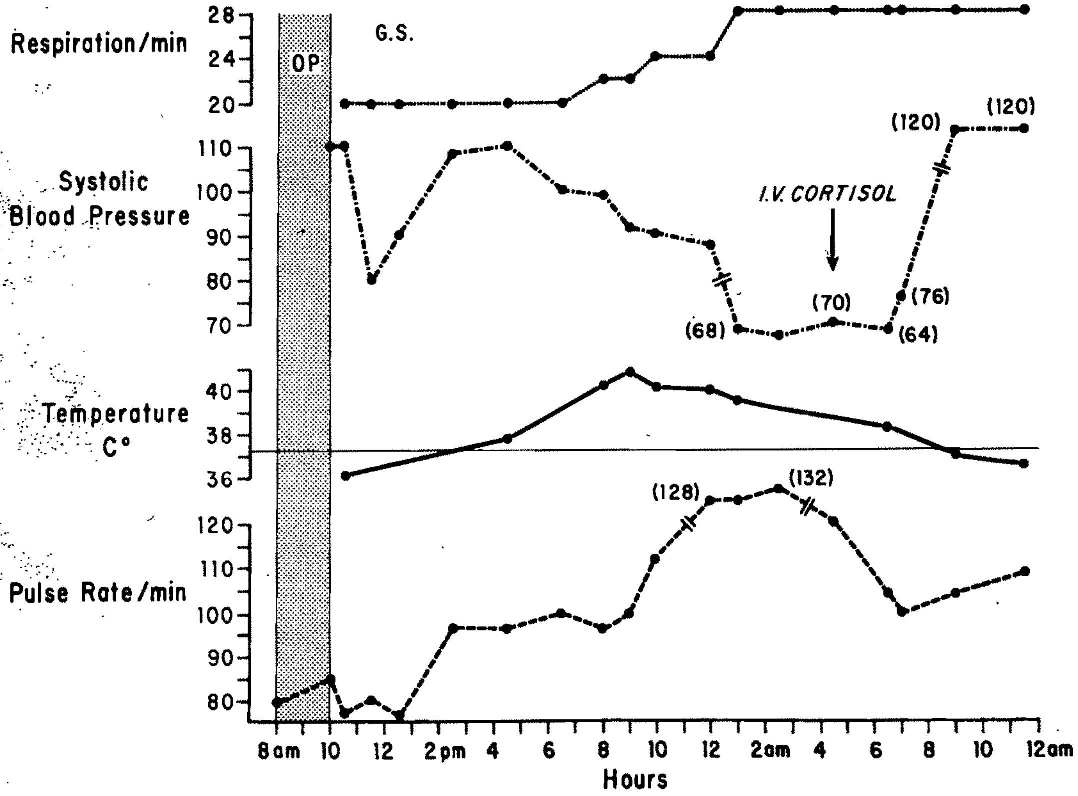

FIG. 1. Outline of physiologic derangements following cholecystectomy in patient G.S., subsequently shown to have Addison's Disease.

TABLE 2. *Plasma and Urine Steroid Data in patient G.S. with Addison's Disease, Demonstrating Lack of Response to Intravenous ACTH*

Date	Plasma Cortisol A.M.	P.M.	Urine 17-OHCS	17-KS
2/4-2/8/68—Dexamethasone	0.5 mg q 6 hr.			
2/6/68	2.0		1.2	7.2
2/6/68—ACTH 50 u IV (8 hrs)				
2/7/68—ACTH 50 u IV (8 hrs)	2.4 (0.9) 11 A.M.		1.4	3.0
2/8/68—ACTH 50 u IV (8 hrs)	7.1		0.7	4.1

The nature of this patient's weakness and vomiting were not recognized. Cholecystectomy was recommended and accepted.

On 1-29-68 cholecystectomy was performed (ECW) without incident.

During the early postoperative hours, emesis occurred. The patient became febrile to 40.2C (Fig. 1). Blood pressure was 98/70 mm Hg and pulse 96/min. Confluent pneumonitis in the right upper lobe was seen. Vigorous pulmonary toilet was begun with little change in temperature. She remained febrile and the blood pressure gradually dropped to 86/54 mm Hg. Hematocrit was 42%.

The patient was transferred to the Intensive Care division. Penicillin and chloramphenicol had been started. The pulse continued rapid, the temperature near 40C and the blood pressure continued to fall to 50 mm Hg systolic. At 4:40 a.m. 250 mg of cortisol hemisuccinate was given intravenously along with one unit of dextran. Serum electrolytes showed serum sodium of 119/mEq/L, potassium 4.3 mEq/L. The patient improved and she received another 250 mg of cortisol at 7:00 a.m. Two hours later her temperature was 37C, pulse 104/min. and the blood pressure 120/80 mm Hg. Lethargy and occasional disorientation continued. She was continued on cortisol hemisuccinate, 50 mg every 6 hours. She was seen by an endocrinologist who made the additional observation that the patient had noted tanning of the skin the previous summer which had failed to lighten as usual. She had noticed deep pigmentation over the elbows and knuckles which became more prominent.

Additional physical examination revealed increased pigmentation of the skin, especially of the elbows, dorsum of the hands and also in the gums. A presumptive diagnosis of Addison's disease was made and the patient was further evaluated with determinations of plasma cortisols and urinary 17-hydroxy corticosteroids (Table 2).

The patient was discharged on her 13th postoperative day, receiving cortisone acetate 37.5 mg daily in divided doses, plus 0.1 mg of fludrocortisone acetate daily. She has remained well.

Comment

In patient G.S. the diagnosis of Addison's disease could have been suggested on the basis of symptoms and abnormal pigmentation if the condition had been considered. She was admitted prior to our present practice of obtaining routine serum electrolytes on admission. Electrocardiography, however, revealed suggestive changes of electrolyte imbalance.

Another example of unrecognized Addisonian crisis is patient M.B. (Fig. 2) with sepsis following drainage of a pelvic abscess and colostomy for ruptured diverticulitis. This patient had borderline adrenal function probably secondary to tuberculosis prior to her acute illness and incapable of normal response to sepsis and the surgery. Here, the adrenal hypofunction was manifested by a toxic psychosis, confusion and lethargy. Adrenal reserve, although marginal, allowed her to be discharged without exogenous steroids, but 15 days later she was admitted with frank adrenal insufficiency. Studies of her adrenal function are presented in Table III.

The following patient is presented to demonstrate iatrogenic adrenal insufficiency.

B.A. #684-637. Admitted on 12-2-56. This was the first University Hospital admission of a 57-year-old female with a seven-year history of polycythemia vera. Over the past three years she had received two courses of radioactive phosphorus, as well as multiple venesections. One and one-half years prior to admission her hematocrit began to drop spontaneously and her spleen began to enlarge. Immature granulocytes and

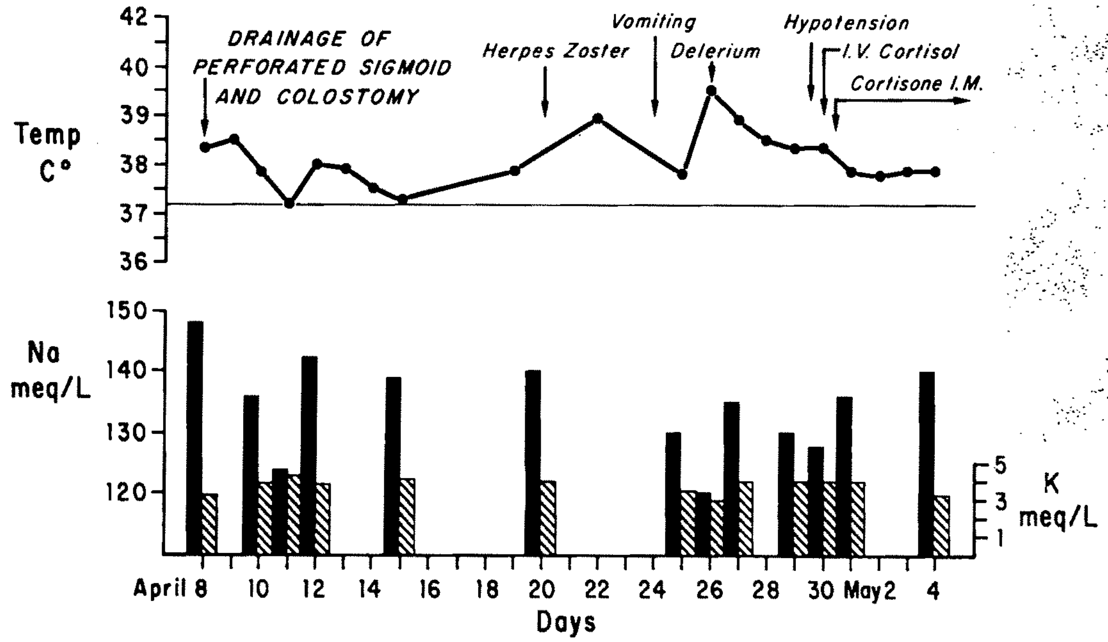

FIG. 2. Outline of clinical course with sepsis, fever and electrolyte changes in patient M.B. Delirium, vasomotor instability and collapse were major signs of adrenal insufficiency (see text) responding to cortisol therapy.

nucleated red blood cells appeared in the peripheral blood. Recently her hematocrit began to fall more rapidly despite therapy with 150 mg cortisone daily. At the time of this admission the hematocrit was 18.5%. Reticulocyte count 6.5%. White count 5,800/mm^3 with 10% blasts. A diagnosis of agnogenic myeloid metaplasia with acquired hemolytic anemia was made.

On physical examination blood pressure was 140/80 mm Hg, pulse 105/min. and respirations 20/min. The patient was a slender, chronically ill, white female with pallor and weakness. Physical examination revealed hepatosplenomegaly. Bone marrow examination was consistent with agnogenic myeloid metaplasia. Osmotic fragility of the red blood cells was noted to be increased.

On 1-13-56 a splenectomy was done under continuous spinal anesthesia. Throughout the operative procedure the patient's blood pressure ranged from 160/90 to 150/80 mm Hg. Three hours after completion of the surgery the patient's temperature was 39.9C, pulse 124/min. and blood pressure 96/80 mm Hg. Four hours later temperature was 39.4C, blood pressure 68/40 mm Hg. She was nauseated and a nasogastric tube drained moderate amounts of gastric contents. She was transfused with whole blood and given intravenous fluids. Blood pressure continued at hypotensive levels. Urinary output was scant. At 2:25 a.m. the following morning 100 mg of cortisol hemisuccinate was given intravenously with prompt rise of blood pressure and a slowing of the pulse rate. By 7:00 a.m. the patient's temperature had returned to normal and pulse and blood pressure stabilized. The remainder of her postoperative course was uneventful and she was continued on cortisone acetate.

Comment

This patient previously reported[8] represents an adrenal crisis brought on by the simple error of omission in writing postoperative orders in a patient known to be on corticosteroids for the hematological disorder. Administration of a single intravenous bolus of 100 mg reversed completely the hypotensive-febrile crisis. It should be the responsibility of the *entire surgical team* to ensure proper postoperative steroid support and look for this omission in the failing patient.

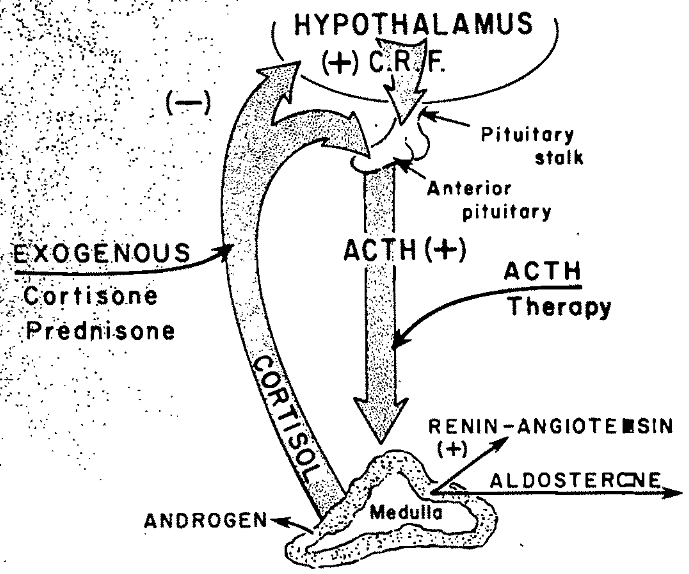

FIG. 3. Normal regulation of adrenocortical secretion. (CRF-corticotropin releasing factor) Note that pituitary insufficiency will have little effect on aldosterone secretion and that ACTH therapy, while causing adrenal hypertrophy, causes pituitary unresponsiveness to changing cortisol concentrations.

TABLE 3. *Plasma and Urine Steroid Data in Patient M.B. Before and After Metyrapone and Intravenous ACTH Administration, Showing Limited Response to Endogenous and Exogenous ACTH**

Date	Plasma Cortisol†		Urine	
	A.M.	P.M.	17-OHCS‡	17-KS§
5/30/71 Admitted				
5/31/71	1.8 mcg			
6/1/71	2.1 mcg			
6/13-14/71			5.5	0.8
6/14-15/71 Metyrapone 750 mg q 4h x 6			2.1	1.4
6/15-16/71		5.4 mcg	1.9	1.0
6/16-17/71 ACTH 25 u IV/8 hrs	0.5 mcg	0.5 mcg	1.0	0.1
6/17-18/71 ACTH 25 u IV/8 hrs			0.4	1.9
6/18-19/71 ACTH 25 u IV/8 hrs	3.6 mcg	4.3 mcg		

*Metyrapone selectively inhibits 11-betahydroxylation during steroid synthesis and is useful in the diagnosis of suspected hypopituitarism.
†n=5-20 mcg/100 ml.
‡n=4-12 mg/24 hr.
§n=4-17 mg/24 hr.

Another patient, D.F. (Table 1) represents the hazard of allowing patient self-treatment, as there was confusion regarding his steroid therapy for arthritis. It was finally ascertained that prednisone had been stopped three months prior to admission, but had been used for a long period prior to cessation. He may represent an ACTH deficiency as pointed out by Danowski.[5] Sepsis and surgery precipitated adrenal crisis. Inadequate preoperative preparation with steroids and no steroids postoperatively were errors in therapy. Nausea, vomiting, abdominal distention, weakness and lethargy, hallmarks of adrenal insufficiency reversed rapidly with resumption of steroid therapy.

Patient M.E.B. (Table I) represented a severe arthritic, who, taking more steroids than her physician prescribed, suffered hypotension, fever, lethargy and apnea, thought to be secondary to gram-negative sepsis, when low oral doses were given. Recovery was prompt after intravenous use of corticosteroids and continued with adequate doses of oral steroids. The mechanism here is undocumented, but may be a combination of ACTH depression by exogenous steroids (Fig. 3) and inadequate steroid administration after admission to the hospital.

The following patient, R.Y., illustrates a category III type, in whom adrenal failure may have contributed to lack of clinical responsiveness by one of several possible mechanisms.

R.Y. #966-109. Admitted on 6-21-73. This was the second hospital admission of this 45-year-old female who was seen in the Emergency Ward on the evening of admission after being transferred from a nursing home. The history obtained was that the patient had been alert and well until shortly before the evening meal, when she developed acute, severe, abdominal pain and sudden collapse. On arrival in the Emergency Ward she was obtunded, but was able to answer simple questions. Her past history revealed that she had been thought to have multiple sclerosis since July, 1971 and had previously been admitted for evaluation in March, 1972. Numerous studies were done, following which she was discharged to an extended care facility with the diagnosis of multiple sclerosis. She was next transferred to a nursing home on hydrochlorothiazide 50 mg daily, KCl elixir 20%, ACTH gel 10 units twice daily.

Temperature on admission was 39.8C. P. 132/min. B.P. 160/40 mm Hg. Hematocrit 40%. White count 18,700/mm^3 with a shift to the left. Physical examination revealed heart and lungs to be clear. The abdomen was distended, rigid and silent. Pelvic and rectal examinations were unremarkable. Stool was negative for occult blood. A Foley catheter was placed and yielded only 10 ml of urine. Urinalysis revealed many white cells and red cells. Serum electrolytes revealed a sodium of 150 mEq/L, potassium 1.7 mEq/L, chlorides 85 mEq/L, CO_2 42 mmoles/L, glucose 265 mg/100 ml, BUN 23 mg/100 ml, and abdominal and chest films revealed only a distended stomach without evidence of free air.

It was the impression of the examining physicians that she had a perforated viscus. At laparotomy no abnormality was found. During the surgery great difficulty was encountered in maintaining the blood pressure, requiring vasopressors and she was given 250 mg of cortisol hemisuccinate. It was thought that her lack of response was secondary to gram negative sepsis of the urinary tract. Urine culture revealed over 100,000 colonies of *Coli aerogenes*. She was started on penicillin and chloramphenicol postoperatively, as well as cortisol hemisuccinate 100 mg every 6 hrs. Temperature remained elevated and she remained hypotensive, requiring large infusions of fluids with vasopressors. With an episode of pulmonary edema, she was digitalized. The diagnosis of relative adrenal insufficiency was postulated and she was given increasing amounts of cortisol. She improved and temperature returned to normal. She was restarted on ACTH gel 15 units t.i.d. and was discharged improved on her 17th postoperative day.

This patient, receiving ACTH for multiple sclerosis, was admitted with fulminating gram negative sepsis of urinary tract origin, and probably had chronic hypercorticism on admission, but this was not documented. She represents hypothalmic-hypophyseal insufficiency produced by prolonged ACTH administration rather than true adrenal failure. Although 400 mg/24 hrs. of cortisol should have been adequate for physiological replacement, the need for additional amounts, given along with other therapeutic measures, is difficult to evaluate. With severe sepsis, increased amounts of steroids are sometimes needed, and for a longer period, before stabilization is observed.

Discussion

Hypofunction of the adrenal cortex is brought about by a number of mechanisms involving destruction of adrenal tissue. These include granulomatous infections, autoimmune atrophy, adrenotoxic drugs, such as O,P'DDD, inborn errors of metabolism, ACTH deficiency, metastatic tumors, amyloidosis, adrenal hemorrhage such as seen in the Waterhouse-Friderichsen syndrome, anti-coagulant therapy,[4] and iatrogenic suppression. Danowski[5] and Liddle[12] point out that a brief (up to several weeks) administration of pharmacological doses of cortisol or synthetic glucocorticoids results in a prompt suppression of ACTH secretion which will recover rapidly after the exogenous steroids are withdrawn. If, however, long term therapy of a year or more has been used, then a true deficiency of ACTH occurs, which may persist for many weeks after the hypercorticoid state itself has been corrected. The subsequent adrenal responsiveness lags behind the resumption of normal ACTH production by several weeks. In general, the longer and the more intense the exogenous corticosteroid therapy, the more likely the patient is to be dependent on steroids after their cessation.

Knowlton[10] and Thorn[29] have summarized the

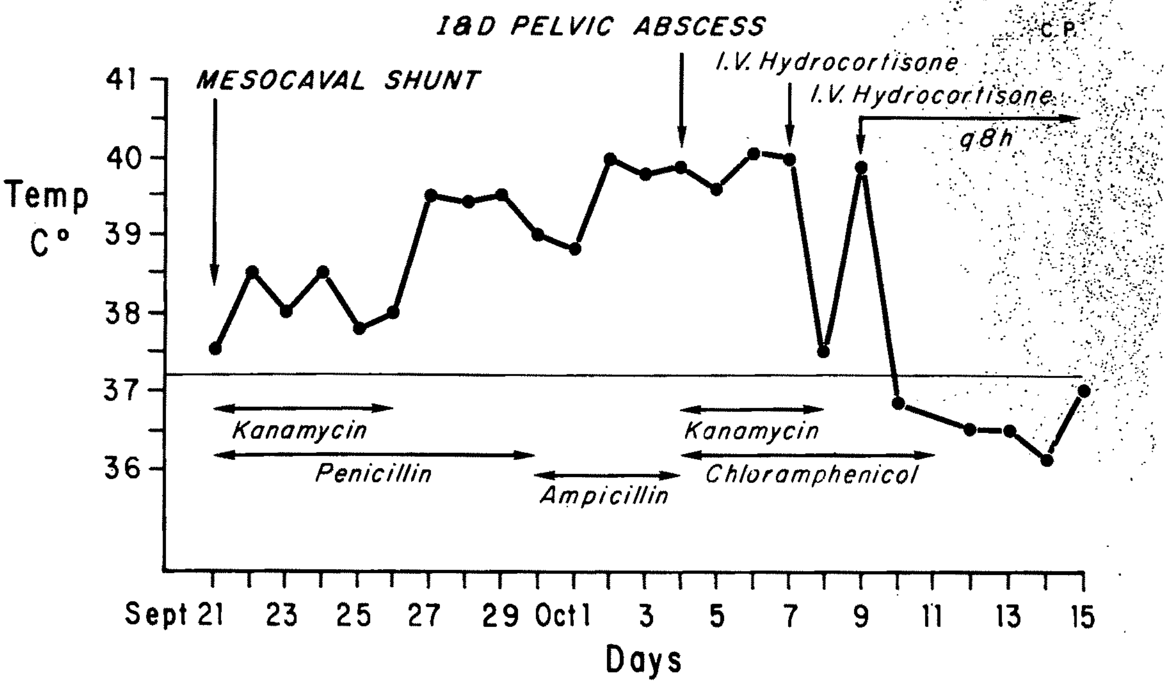

FIG. 4. Outline of clinical course of patient C.P. with prolonged illness, surgery and gram negative sepsis, responding to steroid administration, successfully discontinued later.

symptoms and the usual abnormal findings in Addison's crises. In addition to the classical symptoms of cortisol hyposecretion, exhibited by several of the patients in the preceding case summaries, a variety of central nervous system symptoms can be observed, such as mania, paranoid psychosis, acute brain syndrome and so-called toxic psychoses. This is particularly well illustrated by case M.B. whose delirium and mental aberrations coincided with clinical deterioration manifested by increased fever, hyponatremia and circulatory collapse. Her mental aberrations and toxic delirium took several days to clear after steroid replacement.

The role of sepsis, particularly of the gram-negative type, on steroid metabolism has been reviewed by Beisel and Rapoport.[2] They point out that interpretation of changes in serum cortisol* during infection must include a consideration of diurnal periodicity, plasma protein binding factors, and changing rates of both steroid secretion and degradation. During uncomplicated acute infectious illness, the earliest measurable change in plasma hydroxycorticosteroid (17-OHCS) is the loss of diurnal variation. Under situations of acute infection, cortisol secretion rates are shown to be increased 1½ to 6 times normal. In chronic illnesses, adrenocortical secretion is generally depressed, although most data are based on the studies of patients with tuberculosis. The exact mechanism is not known. It is not related to destruction of the adrenal cortex except in unusual circumstances by metastatic tumor or amyloidosis.

Plasma cortisol levels are noted to be elevated in acute surgical stress, severe infections and infection-induced shock.[16,17] Done[7] has pointed out that plasma cortisol levels increased progressively during the agonal periods in acute fatal illnesses. In moribund patients, it has been noted that degradation of plasma cortisol was shown to be delayed at a time when plasma 17-OH corticosteroids could be raised still further by ACTH administration.[25] Changes in peripheral cortisol metabolism during infection, therefore, may involve mechanisms distinct from those involving depressed activity of hepatic enzymes.[25]

Hemmorrhagic necrosis of the adrenals during acute meningitis has long been observed and is accompanied by low plasma cortisol values.[11] Bacterial toxins, anaphylaxis, generalized toxemia, endotoxin, in combination with epinephrine, and the Shwartzman reaction have all been implicated in the pathogenesis of hemorrhagic adrenocortical necrosis. It may also be a local manifestation of disseminated intravascular coagulation in the presence of shock. Melby[16] demonstrated that large doses of bacterial endotoxin produced a maximal increase in glucocorticoid secretion. Normally ACTH secretion by hypophyseal mechanisms in surgical stress appears to take precedence over the normal feedback regulatory control. Pituitary stimulation may, however, be less than maximal during chronic infections or overwhelming sepsis, for in both, an additional adrenal response may be elicited by exogenous ACTH. The mechanisms through which an infectious process, a bacterial pyrogen or exogenously produced fever serves to stimulate hypophyseal centers remains unknown. It may require mediators released from cells such as leukocytes.[17]

Patients with a variety of acute generalized infections show a relatively limited transient increase in the adrenal output. Less is known concerning the serial progression of adrenal changes as an infectious illness persists or worsens. A depression of adrenal secretion or lack of responsiveness to ACTH may develop during severe or prolonged infection. High plasma cortisol levels found during septicemia, secondary to gram negative organisms, results principally from a *failure* in hepatic clearance and metabolism, rather than from any extraordinary increase in adrenal secretion.[2] Braunstein and Yamaguchi[3] demonstrated cortisol lipid depletion commonly found in patients severely stressed.

Oaks,[21] Lillehei,[13,14] Deitzman,[6] Spath,[27] Weil,[20,30] Alho,[1] Rokkanen,[24] and others[9,11,19,22,23] have postulated the mechanisms of action of the corticosteroids in shock and sepsis. Lillehei presents evidence that the corticosteroids cause vasodilation in gram negative shock in several ways: 1) by slowing nerve impulse transmission in postganglionic sympathetic nerves; 2) by preserving the integrity of small vessels avoiding leakage into the microcirculation; and 3) by decreasing platelet adhesiveness and preserving their integrity, an important factor in preventing or correcting stagnant anoxia in the microcirculation. He also points out that almost always in shock the adrenal cortex responds with increased cortisol output for physiologic needs, just as the adrenal medulla increases its epinephrine output. For therapeutic maneuvers, however, large doses of steroid are needed. These authors also point out that methylprednisolone potentiates the effect of isoproterenol and the treatment of shock requires dosages in the order of 30 mg/kg repeated in 2-4 hours. Spath[27] in an experimental study in dogs revealed that glucocorticoids did not prevent splanchnic vasoconstriction, but appeared to stabilize lysosomal membranes preventing lysosomal release of acid hydrolases and other proteolytic enzymes. They, in contrast to Lillehei and others, could not demonstrate vasodilatation or a positive inotropic effect. Rokkanen[24] studied 29 patients in shock with severe trauma, of whom one-half received in a random fashion, pharmacologic doses of methylprednisolone. Although the steroid treated group demonstrated hormonal effects, such as elevated glucose levels, diminished sodium and sodium-potassium ratio in the urine, and possible increased catabolism, the only significant therapeutic difference between the groups was a diminished incidence of fat embolism in the steroid treated group. In another study, Alho, Motsay and Lillehei[1] stressed that the modifying effects of the treatment of shock with glucocorticoids on the lysosomal enzyme changes may be due to improved capillary profusion or membrane stabilization. Schumer[26] measured the release of histamine from mast cells exposed to endotoxin and proposed that steroids exert their effect by interfering with the endotoxin-induced immune reaction by decreasing either complement or complement fixation, thus preventing the production of anaphylatoxin or other shock toxins. Lefer[11] has recently demonstrated a myocardial depressant factor (MDF) in the blood of shock animals, thought to be a biologically active peptide released by hypoxia and ischemia from the pancreas. Glucocorticoids are thought to have a potentially beneficial effect by preventing lysosomal disruption and the formation of MDF.

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*In this paper we use "plasma cortisol" and "serum cortisol" interchangeably because comparable results are obtained from both sources as long as red cells are removed promptly.

Evaluation of Adrenal Insufficiency in Surgical Patients

Because it is a rare disorder, it is not surprising that adrenocortical insufficiency is not considered more often in a differential diagnosis. Patients should be questioned and examined for evidence of tuberculosis, autoimmune diseases, deficiencies of the pituitary-target organ axis, and a history of chronic therapy with steroids in the past two years.

Whenever adrenocortical insufficiency is suspected, a serum sample for cortisol determination should be obtained before therapy. A low value in an already stressed but untreated patient virtually establishes the diagnosis. Under less urgent circumstances a fasting early morning serum cortisol determination, followed by an intravenous injection of 0.25 mg of Cosyntropin, with a second serum cortisol drawn exactly 30 minutes later, will help establish the diagnosis.[28] In normal persons, the test produces at least a doubling of the serum cortisol, while there is little or no response in a patient with primary adrenal failure.

If adrenal failure secondary to hypopituitarism is suspected, more elaborate testing will be needed. This may be delayed until after necessary medical and surgical treatment has been given. A chronically unstimulated normal adrenal may require 3 days of corticotrophin stimulation. After this a metyrapone test will establish whether or not the pituitary can increase its secretion of ACTH (Fig. 1).

It should be emphasized that a *pretreatment serum cortisol* should be obtained whenever possible. If the *serum* is separated from the whole blood promptly, the test will be valid even if the sample has to be kept in a refrigerator for a week-end or mailed to a distant laboratory.

Because it is of lifelong importance to the patient, a precise diagnosis of adrenal function should be made whenever possible.

Therapy

Fortunately, adrenal dysfunction is rare and its therapy specific, but in life-threatening situations the surgeon must be able to utilize therapeutic maneuvers to allow his patient to withstand the stress of infection and surgery by effective preoperative preparation, steroid maintenance during surgery and on into the postoperative period.

In endotoxic shock, the data of Weil[20,30] indicate that early therapy is important. In the human situation there is usually continued liberation of endotoxin. Here, corticosteroid therapy should be undertaken even though the time of initiation is later in the course of the disease. Pharmacologic doses of corticosteroids are required.

In non-emergency situations for patients with partial or complete adrenal insufficiency, repair of hypovolemia, hyponatremia and hyperkalemia should be begun promptly. Large doses of cortisol given initially (200–300 mg daily, beginning with 100 mg intravenously) will have sufficient mineralocorticoid effect, but as physiologic doses of the glucocorticoid are reached, a mineralocorticoid should be added. Fludrocortisone is the drug of choice to correct the lack of normal aldosterone secretion. When aldosterone secretion is adequate, as in pituitary insufficiency, only cortisone will be needed.

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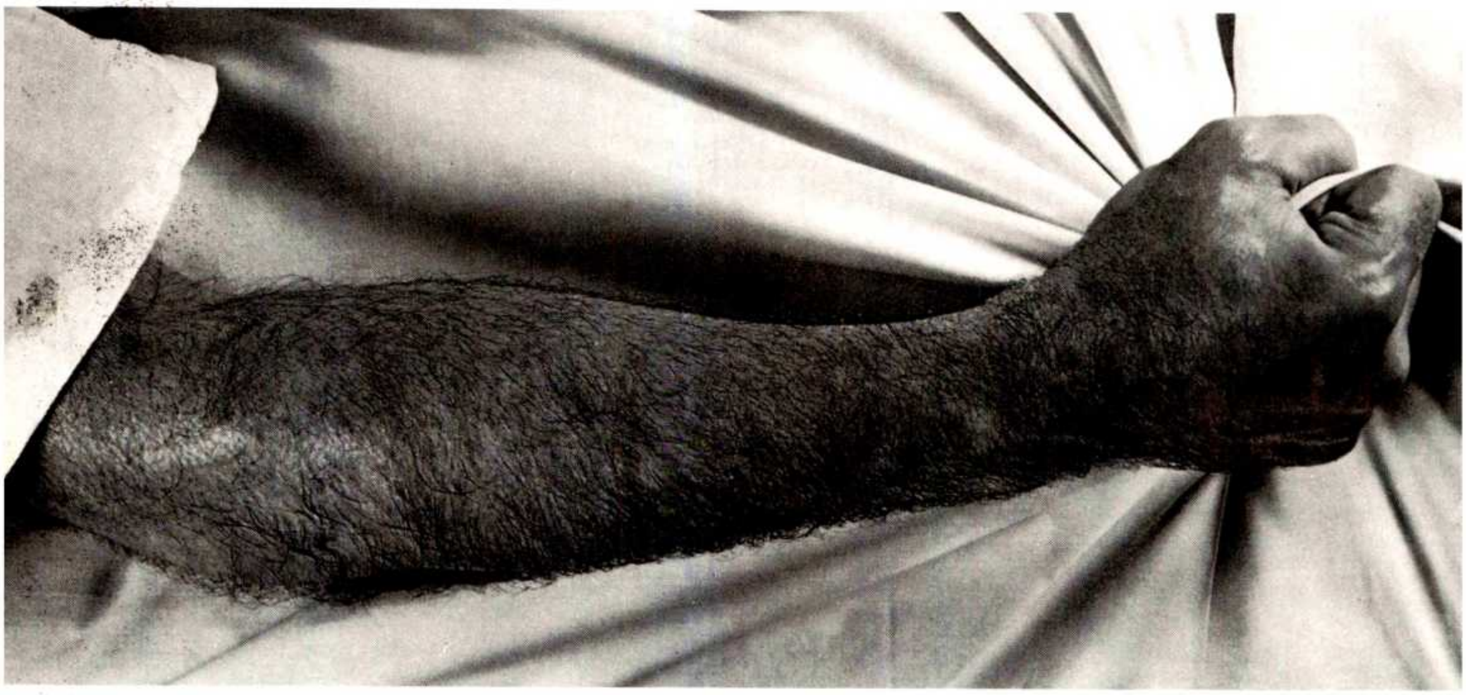

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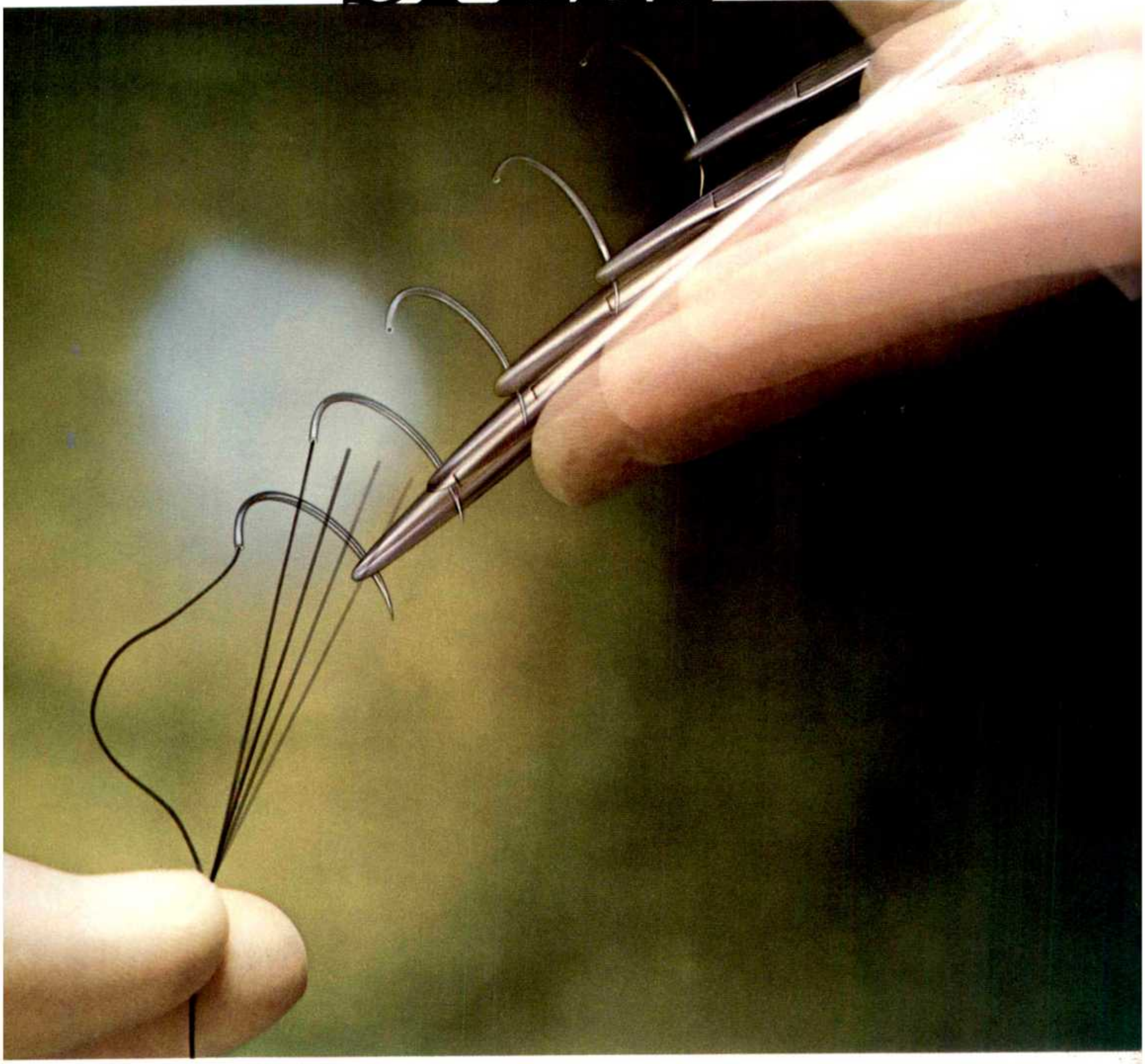

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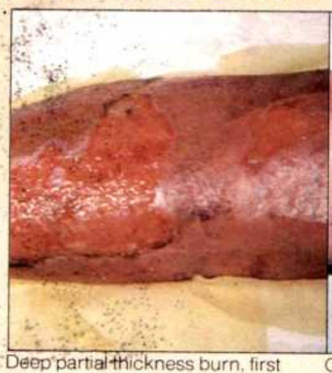

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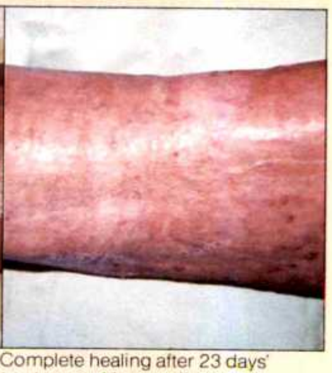

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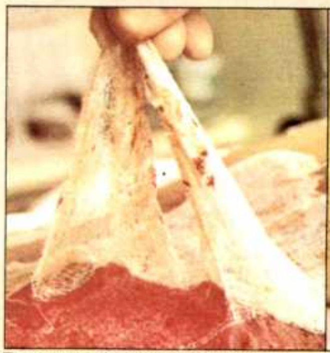

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*Animal data are not intended to imply the same effect in humans. Human studies are now under evaluation.

†Both SCARLET RED and XEROFORM are nonadhering dressings from Chesebrough-Pond's Inc.

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2. Salomon, J.C., Diegelmann, R.F. and Cohen, I.K.: Surg. Forum 25:516, 1974.

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Abdominal Aneurysm and Horseshoe Kidney:

A Review

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Two patients with aortic abdominal aneurysms in association with horseshoe kidney are presented, making a total of 34 cases recorded in the literature. In 29 patients, the aneurysm was resected and five patients were non-resectable. Because of the abnormalities in vascular supply to the abnormal kidney, it is important to diagnose the combination of aneurysm and horseshoe kidney preoperatively. An error in diagnosis should be unusual if an intravenous pyelogram is routinely obtained on all patients. This study may reveal abnormalities which will allow the diagnosis of horseshoe kidney to be made or suspected. If the intravenous pyelogram is abnormal, it should be followed by an aortogram. This may substantiate the diagnosis of aneurysm and horseshoe kidney and provide the necessary detailed information regarding the pattern of blood supply and its relationship to functioning tissue. The amount and disposition of functioning renal parenchyma may be further amplified by renal scan. If this sequence is followed, the unanticipated combination of abdominal aneurysm and horseshoe kidney should be rare.

AN EXTENSIVE REVIEW of the literature has yielded only 32 cases of abdominal aortic aneurysm and horseshoe kidney. As the incidence of horseshoe kidney occurs in one to 600-1800 individuals,[25] it is probable that this combination has been encountered more frequently than these numbers indicate. Often, the first experience, is unanticipated and without a full appreciation of the difficulties which may be encountered.

The purpose of this report is to relate two new patients and to summarize the collected experience to help clarify the difficulties in preoperative diagnosis, decisions regarding resectability, preservation of renal function and blood supply and surgical management of the fused kidney.

Case Reports

Case 1. U.H. #03-75-86. E.W., a 68-year-old retired carpenter, was referred for an abdominal aneurysm found on routine physical examination two to three months prior to admission. There had been no symptoms referable to the aneurysm. A 10-year history of hypertension had been under treatment for three months. On physical examination, the blood pressure was 145/85, pulse 88 and regular with respirations of 18. A palpable, pulsatile, abdominal mass was noted to the right of the midline, without tenderness or rebound. In addition to hypertension, the patient exhibited emphysema and possible diabetes. In July, 1963, the patient underwent laparotomy for abdominal aneurysmectomy.

At operation a horseshoe kidney was found fused over the bifurcation of the aorta. From the common iliac, slightly to the left of the crotch of the normal bifurcation, there was a rather large renal artery supplying the inferior pole of both kidneys. There was a whitish area in the mid-portion of the fusion of these two kidneys suggesting a relatively avascular area. The ureter could be identified on the left retroperitoneally in the usual position, but posterior to the isthmus of the horseshoe attachment; the right ureter was not well seen. The renal arteries could be palpated superiorly, but were not directly visualized. Both renal veins were visualized and not disturbed. The horseshoe kidney was divided at the lower poles, taking care to distribute the blood supply from the accessory renal artery to both lower lobes in what appeared to be an equitable fashion. The two sides of the transected kidney were oversewn with a double row of 3-0 plain catgut which controlled all bleeding. The aneurysm was excised and replaced in the usual fashion with a 22 mm Dacron graft. The surfaces of the transected kidneys were covered by means of retroperitoneal tissue and the posterior peritoneum was closed. The patient remained well following discharge 13 days postoperatively until his death 10 years later of carcinomatosis secondary to carcinoma of the lung.

Case 2. U.H. #18-65-81. H.S., a 69-year-old man, had been seen by an osteopath for several months for left thigh pain. After a particularly severe episode, he saw a chiropractor who, obtained x-rays and told the patient he had an abdominal aneurysm. He was advised to see a physician, and a surgeon, who, after obtaining an aortogram, found that the patient's abdominal aneurysm was associated with a horseshoe kidney. Two renal arteries were noted to each kidney, and there was some question whether the left renal arteries arose from the aneurysm. An exploratory laparotomy was performed in June, 1971, approximately four months after the initial x-rays. After a lengthy dissection, several vessels were noted to

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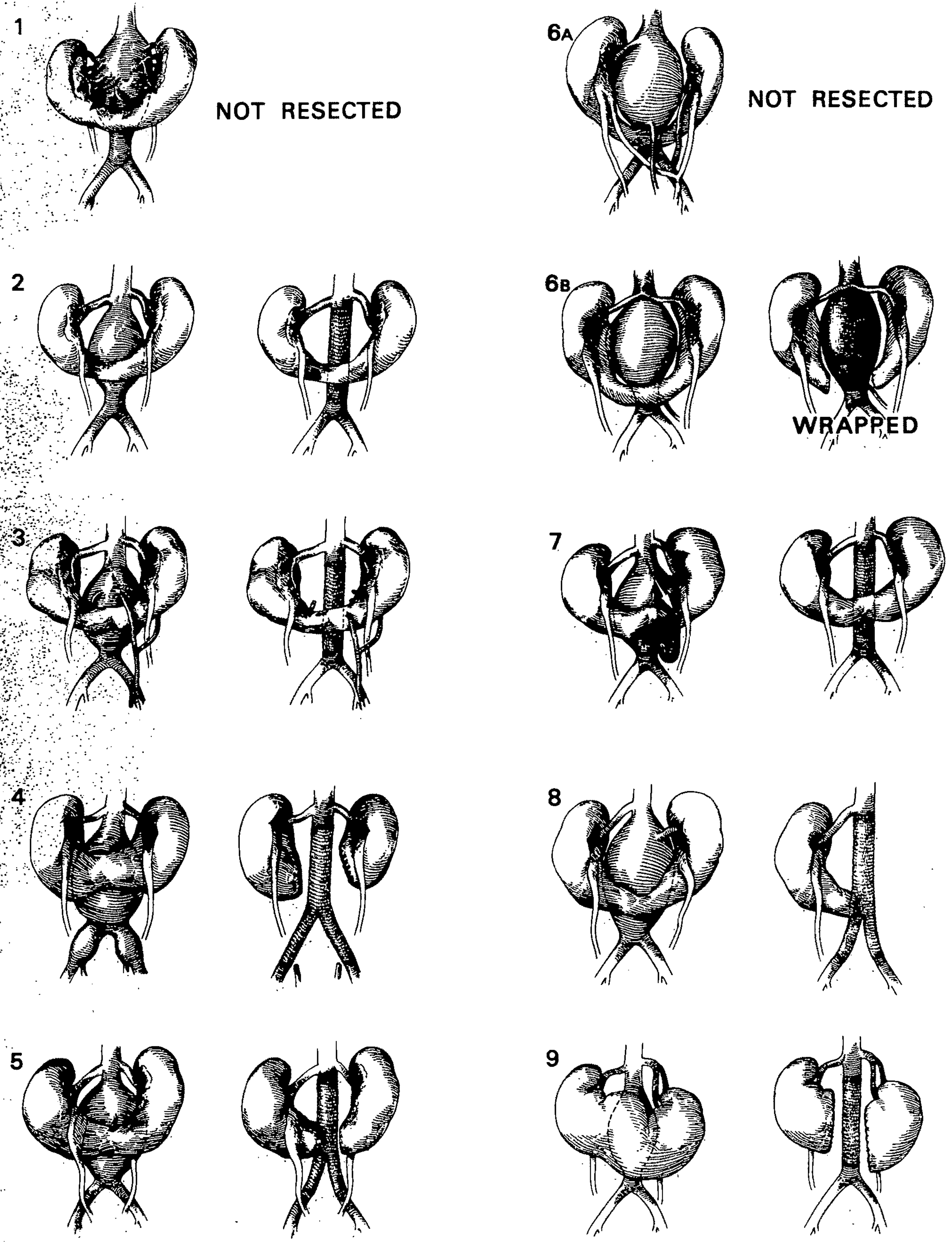

FIGS. 1a-d. Operative findings and operative procedure are shown. The diagram in the original article or the description of operative findings has bee used to construct this composite. The drawings are identified sequentially and correspond to Table 1 and the References at the end of th article.

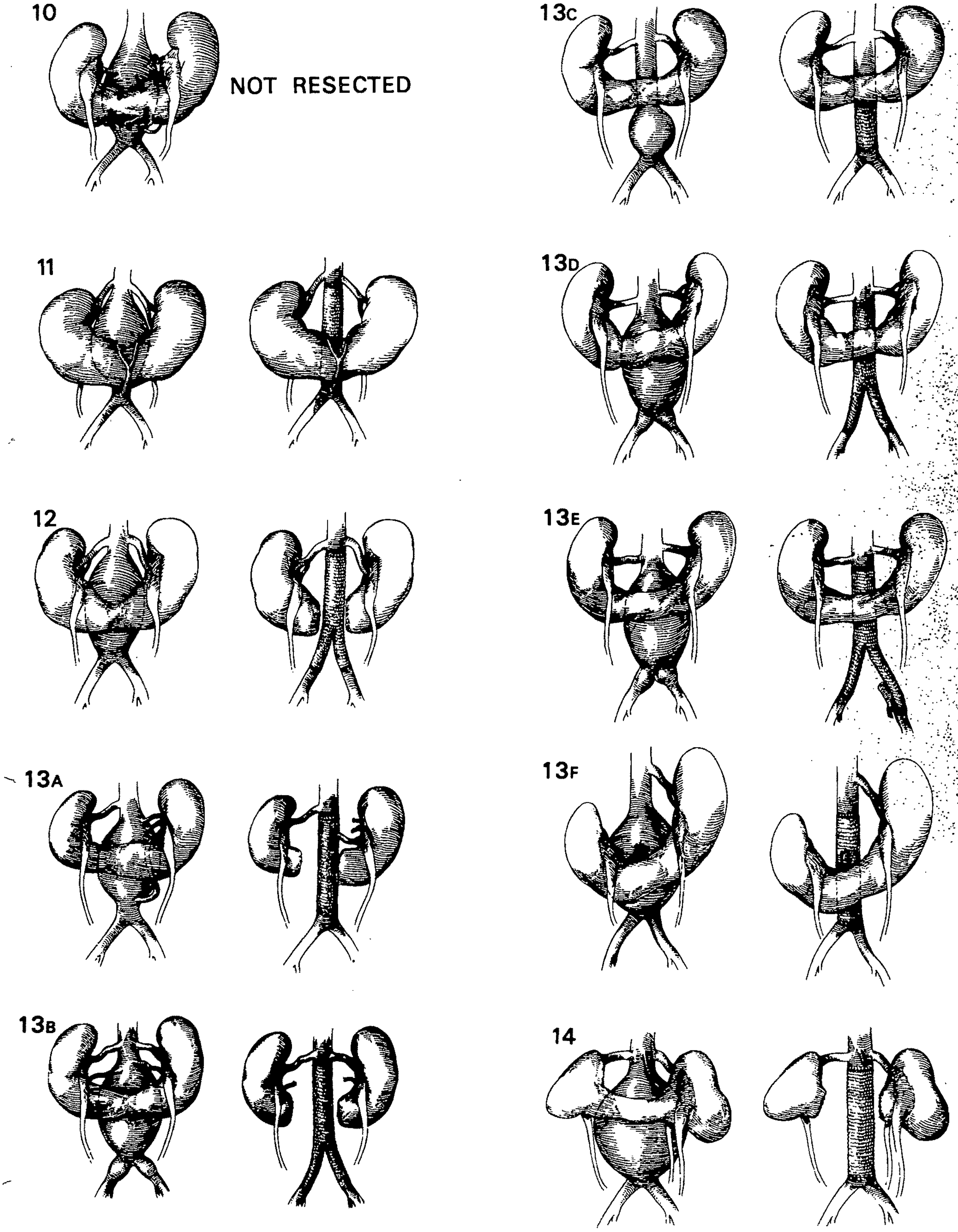

FIG. 1b.

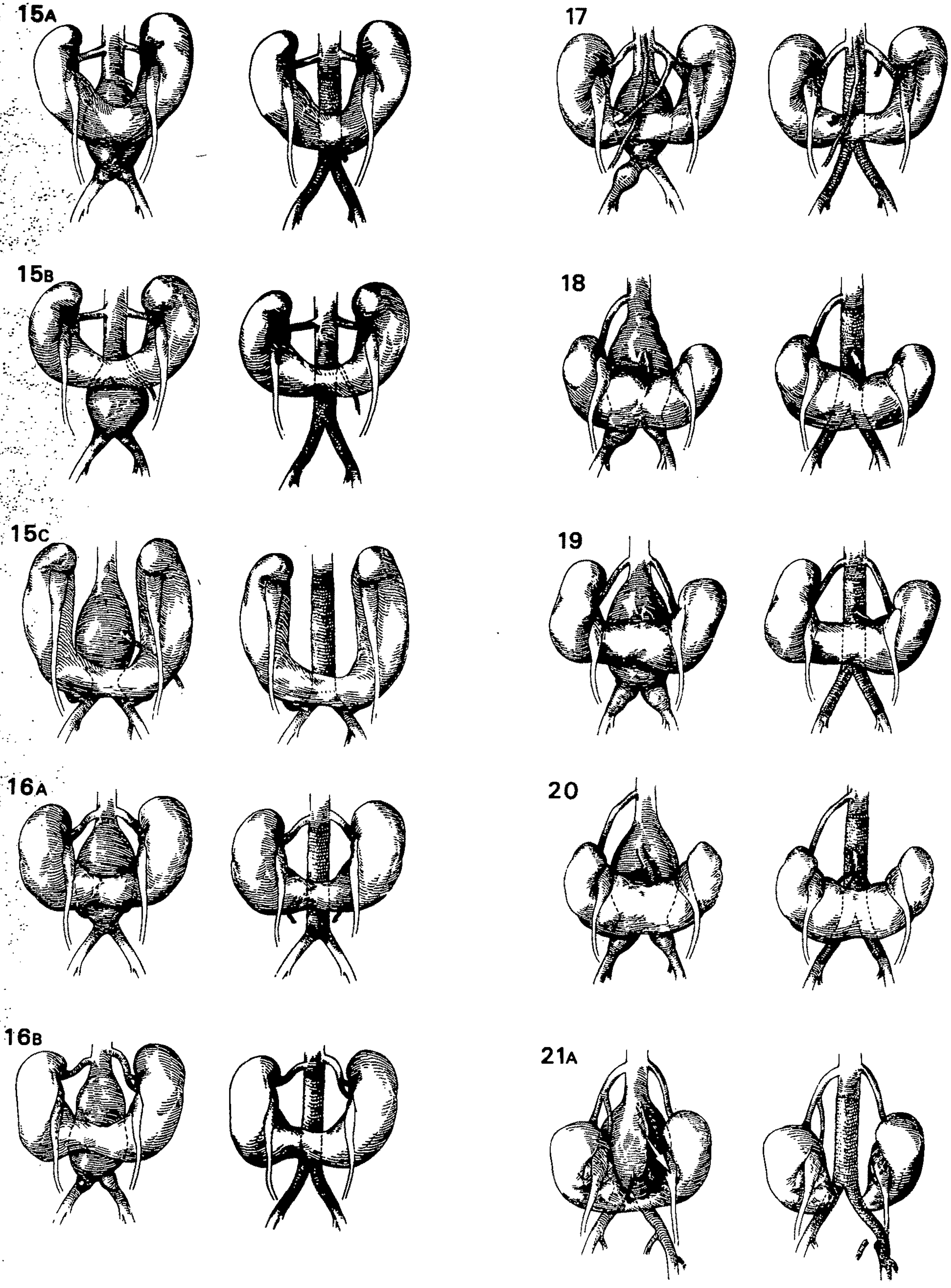

FIG. 1c.

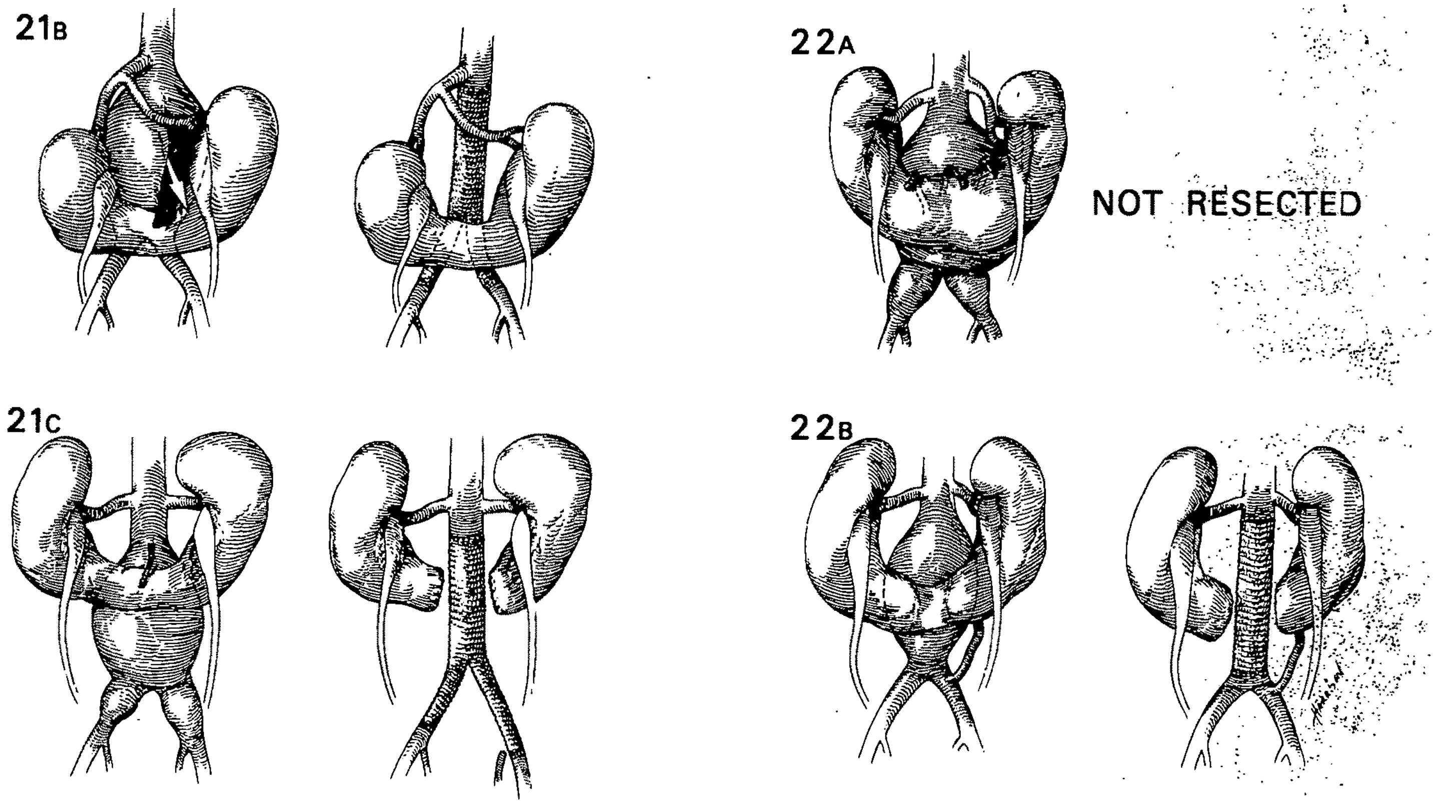

FIG. 1d.

arise from the aneurysm and no further procedure was attempted. Postoperatively, the patient was seen at three-month intervals. After six months, the aneurysm, though asymptomatic, was noted by x-ray to have increased in size. The patient was admitted to the University of Washington Hospital for consideration of further surgery. Blood pressure was 120/95 with good femoral pulses. The abdomen was soft without tenderness or guarding. A firm, pulsatile mass was noted to the left of the umbilicus. The remainder of the examination was not unusual. Laboratory data was not remarkable. A repeat aortogram was compared with the aortogram taken six months previously, and revealed a total of five blood vessels to the main bulk of the renal parenchyma.[22a] An accurate definition of the origin of these vessels from the aorta relative to the aneurysm, was difficult, although it was tentatively concluded that at least three came from the bulk of the aneurysm. Having discussed all possibilities with the patient, an exploratory laparotomy was undertaken in February, 1972.

Because of previous retroperitoneal dissection, the operation was difficult and tedious. Because of the aneurysm's bulging to the left, the left colon was completely mobilized medially, and dissection of the renal capsule was performed. A number of renal arterial vessels were identified. The proximal two right renal vessels were above the aneurysmal portion of the aorta. The remaining three vessels, of which only two could be identified, were seen to arise from beneath the isthmus of the kidney and from the aneurysm.

A splenectomy was performed in an attempt to mobilize the splenic artery to have it provide the arterial supply to at least one of the renal vessels coming from the aneurysm. This approach had to be abandoned because of the patient's obesity and inadequate length of the splenic artery.

The isthmus of the kidney was 2–2.5 cm in thickness and was obviously functioning parenchymal tissue. An attempt to mobilize the inferior portion of the kidney to approach the vessels from beneath was limited by the presence of the ureters which arose and descended anteriorly. An attempt to mobilize the right side of the horseshoe kidney for renal artery access was impossible because of multiple renal veins exiting to the right towards the inferior vena cava. After a prolonged and extensive dissection, it was felt that because of the difficulty of aortic access combined with inadequate control of possibly serious blood loss plus the risk to renal function (both from interference with arterial and/or venous patterns) that removal of this aneurysm was not warranted. This had been discussed with the patient prior to the operative procedure. He had expressed no desire to go through the rigors of renal dialysis with possible renal transplantation if the aneurysm could not be resected without undue risk to the kidney.

The postoperative course was complicated by a left subphrenic collection of pancreatic juice which was drained via a left subcostal approach. This drained intermittently for a prolonged period before it stopped. The patient remains asymptomatic to date.

Comment

These two cases represent the extremes which may be encountered. Case 1 represents the ideal situation for "cure," while Case 2 exemplifies the non-resectable situation.

Review of the Literature

An analysis of these two cases together with the 32 cases previously reported in the literature was felt necessary in order to obtain some concept of the variations which one might anticipate with this combination of lesions.

In the collected series, the average age of the patients was 60 years, ranging from 48 to 76 (age was not recorded in 3 patients). Symptoms were not a prominent part of the clinical picture. From the data available, no correlation with hypertension could be made. The diagnosis preoperatively

AUTHOR	SIZE	RESECT	KIDNEY	RRA	LRA	ANOM	DX	IVP	GRAM	AGE	SEX	FOLLOW
1. Julian	small	No	Intact	Multiple small vessels from aneurysm to all parts of the kidney			No	Yes	No	NR	NR	NR
2. Phelan	10 cc	Yes	Intact	Above	Above	None	No	Yes	No	57	M	5 Mo. a & w
3. Dahlen	NR	Yes	Intact	NR	NR	Several small sacrificed	No	Yes	Yes	60	M	Death, 1 day
4. Szialagyi	NR	Yes	Divided	NR	NR	NR	No	No	Yes	58	M	NR
5. Wilder	6 cm	Yes	Divided	Above	Above	1 small isthmus branch sacrificed	Yes	Yes	Yes	48	M	Working w/o sympt.
6a. Falor	8 cm	No	Intact	From aneurysm	Left Iliac	The left as noted	Yes	Yes	Yes	62	F	6 yr a & w
6b. Falor	9 cm	wrapped mersilene	Divided	Single trunk from aneurysm split to supply both halves of the kidney			No	No	Yes	61	M	2-1/2 yr a & w
7. Mannick	NR	Yes Ruptured	Intact	NR	NR	NR	No	No	No	NR	NR	A & W
8. Lynn	"Large"	Yes	Left resected	Above	From aneurysm	None	Yes	Yes	No	48	M	2 yrs a & w
9. Minken	7 cm	Yes	Divided	Above	Above	None	No	No	Op	59	M	NR
10. Cox	NR	No	Intact	Multiple small vessels from aneurysm to both halves of kidney			Yes	Yes	No	71	M	NR
11. Killon	NR	Yes	Intact	Above	Above	Aortic crotch to isthmus	Yes	No	Yes	71	F	3 yr a & w
12. Love	Large	Yes	Divided	Above	Above	None	Yes	Yes	Yes	64	M	6 mo a & w
13a. Scott	NR	Yes	Divided	Above	Distal to aneurysm re-anastomosed to graft	Small left branches sacrificed	No	No	No	71	M	Death-5 yrs
13b. Scott	NR	Yes	Cyanosis Divided	Above	Above	2 from aneurysm sacrificed	No	No	No	58	M	5 yr a &w
13c. Scott	NR	Yes	Intact	Above	Above	None	Yes	Yes	No	58	M	4 yrs a & w
13d. Scott	NR	Yes	Intact	Above	Above	None	Yes	Yes	No	52	M	MI - 3 yr p.o.
13e. Scott	NR	Yes	Intact	Above	Above	None	Yes	Yes	No	67	M	2 yr. a & w
13f. Scott	NR	Yes	Intact	From aneurysm reanast.	Above	Right as noted	Yes	Yes	Yes	69	M	9 mo a & w
14. Sigler	25 cm	Yes	Divided	Above	Above	One to isthmus	No	Yes	No	65	M	33 mo a & w
15a. Cohn	9 cm	Yes	Cyanosis Scan normal	Above	Above	One to isthmus	No	No	No	64	M	5 yr. a & w
15b. Cohn	9 cm	Yes	Intact	Above	Above	None	Yes	Yes	No	61	M	1 yr a & w
15c. Cohn	10 cm	Yes	Intact	Right Iliac	Left Iliac	None	Yes	Yes	No	76	M	3 yr a & w
16a. Marable	10 cm	Yes	Intact	Above	Above	2 small to lower pole sacrificed	Yes	Yes	Yes	62	M	NR
16b. Marable	9 cm	Yes	Intact	Above	Above	None	Yes	Yes	Yes	62	M	NR
17. Press	NR	Yes	Intact	Above	Above	None	Yes	Yes	Yes	72	M	1 mo. a & w
18. Davis	6 cm	Yes	Intact	Above	From aneurysm reimplant.	Left only	Yes	Yes	No	51	M	10 days a & w
19. Kilgore	NR	Yes	Intact	Above	Above	From aneurysm reanast.	Yes	Yes	No	NR	NR	NR
20. Hardy	NR	Yes	Intact	Above	Anast. to graft	No	No	No	No	51	M	1 mo.
21a. Cayten	NR	Yes Ruptured	Divided	Above	Above	None	Yes	Yes	No	62	M	1-1/2 yr a & w
21b. Cayten	NR	Yes Ruptured	No	Above	Above	None	No	No	No	59	M	Death 11 PO da
21c. Cayten	NR	Yes	Divided	Above	Above	1 small isthmus	Yes	Yes	Yes	68	M	5 yr. a & w
22a. Bietz	7 cm	No	Intact	Above	Above	3 from aneurysm	Yes	Yes	Yes	70	M	2 yr a & w
22b. Bietz	6 cm	yes	Divided	Above	Above	Left iliac	No	Yes	No	68	M	2 yr a & w

TABLE 1.

was made in 20 of 34 cases. The association of horseshoe kidney and aneurysm was known in 3 of 5 unresected cases and 17 of 29 resected patients.

Surgical exposure of the aneurysm was facilitated by division of renal substance in 11 cases; the kidney was not divided in 20 patients. In one case, ligation of an anomalous artery resulted in cyanosis of the left half of the kidney which was then resected:[8] In one case, division of an anomalous artery to the isthmus resulted in localized cyanosis. The isthmus was then divided.[13b] Cyanosis was ignored following division of an anomalous artery in one case and the scan later showed normal function.[15a] In those aneurysms not resected, the kidney was divided only once to facilitate wrapping of the aneurysm with mersilene.[6b]

The right renal artery was normal and above the aneurysm in 25 of 34 cases. In three additional cases, it was not specifically recorded, but because the aneurysm was resected, the artery was probably in normal position. In two instances, a main right renal vessel did not exist; the multiple vessels were all of small size.[1,10] In one case, the right renal artery arose from the right iliac artery.[15c] In only one instance did a single right renal vessel arise from the aneurysm supplying the major portion of the right kidney.[13f] A low takeoff from the aorta but above the aneurysm, was recorded in one case and a single trunk, later branching to supply the two halves, was also noted.[6b,21b]

The left renal artery was somewhat more variable with 22 of 34 in normal position above the aneurysm and three probably above but without specific mention. Three left renal arteries arising from the aneurysm required reimplantation.[18,20,13a] Two left renal arteries arose from the left iliac artery.[6a,15c] On only one occasion did a main left renal vessel require reanastomosis from below the aneurysm to the graft. The kidney in this patient was divided.[13a]

In 18 of 34 patients no anomalous vessels were reported. In two additional cases, there were no records, but presumably no anomalous vessels were present. While the main right or left renal artery may have been anomalous, there were no other anomalous vessels. Separate vessels to the isthmus were found in six patients; in three patients these vessels were sacrificed. On one occasion, the total blood supply consisted of a single renal vessel arising from the aneurysm, dividing to supply all portions of the horseshoe kidney. In two instances, the renal blood supply consisted of multiple, small vessels; no specific right or left main renal vessel could be identified,[1,10] On five occasions, there were other anomalous vessels to other portions of renal parenchyma; on three occasions, these vessels were divided; in two instances they were left intact. In only one patient was a vessel anastomosed other than the main right or left renal artery.[29]

Resection was not attempted in five patients for the following reasons. In one instance a single trunk from the aneurysm split to supply both halves.[6b] One patient had the major blood supply to the right kidney arising from the aneurysm which accounted for 80% of the renal substance.[6a] Two patients exhibited multiple smaller vessels from the aneurysm;[1,10] and an additional patient had three major vessels supplying major portions of renal parenchyma arising from the aneurysm in the presence of an isthmus which was obviously functioning.[22a] Obviously, complicated vascular supply to important portions of renal parenchyma raises concern regarding aneurysmal resection which may destroy significant amounts of renal parenchyma or create renovascular hypertension.

The length of followup in all cases varied from 10 days to 6 years. The longest followup was in a non-resected patient.[6] There were no recorded deaths for non-resected patients, however, there was followup on only three of five patients.

Discussion

Variations in the vasculature of the horseshoe kidney are numerous. Consequently, contemplated resection of an abdominal aneurysm in association with a horseshoe kidney poses special problems which in the patient's best interest should be identified prior to exploration. First consideration must be given to the avoidance of the unanticipated combination at laparotomy.

Ordinarily, the presence of an abdominal pulsating mass in the asymptomatic patient, a negative chest x-ray together with AP and lateral films for spine detail showing the typical calcium pattern is adequate for the diagnosis of an aortic abdominal aneurysm. Since about 99% of such aneurysms occur below the renal arteries, the surgeon may feel confident in advising surgery for the appropriate patient without further study. In balancing the possible value of additional information gained versus the expense and morbidity of aortography either by femoral or lumbar approach, it may be reasonable to proceed without further study where the diagnosis and extent of aneurysm is not in question. The authors subscribe to the philosophy that aortography should be reserved for special situations. However, an intravenous pyelogram should be an integral part of the preoperative evaluation for abdominal aneurysm. The diagnosis of horseshoe kidney can almost always be made by an intravenous pyelogram. Additionally, it is a reliable test for gross renal function and gives valuable information about the distribution of functioning renal substance, and the course of the ureters. If the IVP is abnormal, an aortogram should be done. While not in keeping with our experience, up to 50% of IVP's in the presence of aneurysm have been described as abnormal.[23]

While this sequence of workup should largely avoid the intraoperative diagnosis of this anomaly, it is not infallible. In the collected series, the diagnosis of horseshoe kidney was not made in 5 despite instances of obtaining an intravenous pyelogram. However, of these 5 patients, the diagnosis was renal malrotation in three and misinterpreted as normal in the 4th patient. In the remaining patient, the diagnosis was missed despite the fact that both an intravenous pyelogram and an aortogram had been carried out. The intravenous pyelogram revealed renal distortion and displacement, but the diagnosis of horseshoe kidney was not made. In only one patient in the entire series was the diagnosis made without the benefit of an IVP. The aortogram revealed an abnormal renal architecture.[11] While some feel that aortography is the answer to demonstrating the renal vasculature, aortic configuration and horseshoe kidney, in three cases in which aortogram was of satisfactory quality, neither aberrant arteries nor the horseshoe kidney were demonstrated.

Thus, while the diagnosis can be missed with either an IVP or an aortogram alone, if an IVP is done and is abnormal, followed by an aortogram, the likelihood of making the diagnosis as well as defining the surgical problems relating to aneurysmectomy are excellent, and as a corollary, the likelihood of missing the association of the two should be small indeed.

In those situations when the intravenous pyelogram and aortogram leave some question relating to the anatomic details, a renal scan can be used as an additional measure to identify functioning renal tissue.[12]

The surgical challenge is to resect the aneurysm which is a life-threatening lesion, while preserving renal function. Consequently, resectability is determined almost entirely by the vascular patterns to the abnormal kidney. It is for this reason that aortography is of vital importance in planning one's operative approach. The more common varieties of arterial anomalies can be summarized as follows: a single artery to each half of the kidney; a single artery to each half plus an additional artery to the isthmus; two renal arteries to each half and two arteries to the isthmus; and multiple renal arteries (4–10) to all portions of the renal substance.[23] These vessels supplying the horseshoe kidney may arise at any point along the aorta, occasionally from the iliac arteries and in several instances the mesenteric vessels. Most of these variations have been noted in the present review.

As the major components that contribute to the problem are the vascular supply to the kidney and the fused kidney, they must be dealt with together. Obviously, the possible combinations are many. Case 1 exemplified the most favorable situation, *viz,* all renal arteries arising above the aneurysm in the presence of a horseshoe kidney with mainly a fibrous isthmus. This creates no special problem, as a simple division of the isthmus with oversewing of each end to control bleeding can be carried out which then allows resection of the aneurysm and grafting in a routine fashion. The problem of vascular supply becomes compounded when major renal vessels arise from the aneurysm and must be reanastomosed if resection is carried out. If there are small vessels in the presence of major right and left renal arteries, an alternate approach is to sacrifice these vessels if they supply the isthmus area, with immediate resection of the discolored parenchyma, or delayed resection if hypertension develops presumably on the basis of retained renal substance with marginal blood supply. The effect of sacrifice of such small vessels in this situation when additional major renal arteries are present, is not always predictable.

When complicated renal arterial blood supply is combined with an isthmus of renal tissue as thick as the main bulk of renal parenchyma with preoperative demonstration of function, a decision is required in deciding whether resection of the aneurysm is justified in an elective situation. Unfortunately, a complicated vascular pattern with a functioning isthmus are apt to occur together. When severance of the functioning isthmus is not necessary or the arterial supply is arising from areas other than the aorta and thus not complicating access to the aneurysm, aneurysmal resection may be possible with tunneling the graft posterior to the parenchyma.

If multiple, small vessels are demonstrated preoperatively, it is likely that the patient would be considered inoperable. On the other hand, if the situation were unclear, and operation advised, and it was noted that it would be necessary to sacrifice these vessels, most surgeons would consider the aneurysm non-resectable. In such complex situations, one is tempted to consider the possibility of autotransplantation, however, it is unlikely to be feasible. While there is no recorded instance of auto-transplantation for horseshoe kidney, it has been done in the presence of hypertension, ureteral injury, and other trauma.[27,30,35] The methods for temporary preservation are relatively standardized.[31,33] Techniques have applicability in the emergency situation even in hospitals where formal transplantation programs, pulsatile organ perfusion, etc. are not available. Ischemic times up to 600 minutes have been reported with immediate diuresis and even times of 955 minutes have been observed in which renal function has been preserved.[33]

While complete division of all vascular structures and ureters would allow better exposure of small vessels for microanastomosis, it is clear for several reasons that such an approach to this problem would be possible only in the most unusual situation. First of all, while attention justifiably has been focused on the arterial side of the vascular supply to the kidney, the venous drainage is of equal importance in the success of the operation. In general, when the arterial supply is more normal, so is the venous pattern; as the arterial patterns become more chaotic, the venous pattern becomes more inconsistent and is susceptible to the many vagaries of venous drainage in other areas of the body. In Case 2, the failure to resect was conditioned as much by the abnormal venous drainage as the arterial supply to the kidney. Additionally, as only about 40% of patients with abdominal aneurysm die of rupture, an overly-aggressive attitude in such a difficult situation may be difficult to justify.[26] The generalized disease which the arteriosclerotic aneurysm represents allows many other avenues of exodus. Furthermore, the age of the average patient is such that heroic measures would not be readily accepted either by the patient or his surgeon. While a kidney allograft, either at the time of operation or delayed, might be more likely to succeed, few would feel that patients in this age group would be satisfactory candidates except in the presence of an emergency, viz., rupture or threatened rupture when the immediate survival of the patient is at stake.

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The Effect of Dextran on the Lysability of Ex Vivo Thrombi

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The lysability was determined of thrombi formed in Chandler tubes before and after infusion of 500 ml dextran 70 to patients undergoing cholecystectomy. ^{125}I-labelled fibrinogen was given the day before operation. Following incubation of the thrombi in plasmin, radioactivity remaining in the thrombi and released to the supernatant was determined, as well as fibrinolytic degradation products in the supernatant, using an immunoelectrophoretic method. The dextran infusion was found to increase the radioactivity released from the thrombi to the supernatant from 15.5 ± 7.6% to a maximum of 27.3 ± 8.2% four hours after the infusion ($P<0.001$). A corresponding significant rise of the FDP concentration in the supernatant from 16.8 μg/ml to 44.1 μg/ml was found at the same time. After 24 hours the radioactivity had returned to initial values. The results indicate that dextran infused into patients during surgery increases the lysability of thrombi. It is suggested that this finding at least partly explains the antithrombotic effect of dextran.

DEXTRAN with an average weight of 75 000 as well as 40 000 has been found to prevent thromboembolism both experimentally[6,13] and postoperatively in humans.[2,5,9,15,18] The antithrombotic effect has partly been ascribed to the decrease of platelet adhesiveness obtained after dextran administration,[4,8,11] partly to the flow improving properties of dextran.[15] Dextran has been shown to initiate fibrin precipitation.[1,19] The morphology of the precipitated fibrin differs from that of normal fibrin by being coarser and more variable in size than normal.[23,29] This has been suggested to make fibrin more easily dissolved by fibrinolytic agents.[23,29] The purpose of this study is to further elucidate the mechanisms of the antithrombotic effect of dextran by studying the lysability of ex vivo thrombi formed in the presence of dextran.

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Material and Methods

Eighteen patients (14 women and four men) were studied before and after cholecystectomy. The day before operation they received an intravenous injection of fibrinogen labelled with ^{125}I according to the method of McFarlane.[22] During the operation 500 ml of 6% dextran 70 in normal saline (Macrodex®, Pharmacia, Uppsala, Sweden) was infused in one hour to 12 of the patients. Six patients served as controls and did not receive dextran. Blood samples were collected before, immediately after and at 1, 2, 4 and 24 hours after the dextran infusion. Two ml of blood without anticoagulant was rotated in Chandler tubes[10] at 30 rpm for 1 hour. The thrombi formed were then removed from the loops into plastic tubes, centrifuged for 20 minutes, and after the addition of 2 ml isotonic saline or the same volume of saline containing 4.2 CTA units of plasmin (Novoplasmin®, Novo, Copenhagen), were incubated for 80 minutes at 37 C. After further centrifugation the radioactivity in the thrombus and the supernatant was determined in a y-spectrometer (Wallac). In the supernatant the concentration of fibrinolytic degradation products (FDP) was also analysed using an immunoelectrophoretic method.[24]

The amount of FDP in simultaneously collected blood samples was determined in 12 patients using the same immunoelectrophoretic method. The factor XIII level in blood was determined in five patients in platelet-poor and platelet-rich plasma, using the method of Lorand et al.[20] modified according to Henriksson et al.[14] The dextran concentration was determined in seven patients with the anthron method.[16] The determinations were kindly performed by AB Pharmacia, Uppsala, Sweden.

To study the effect of dextran in vitro, blood from four

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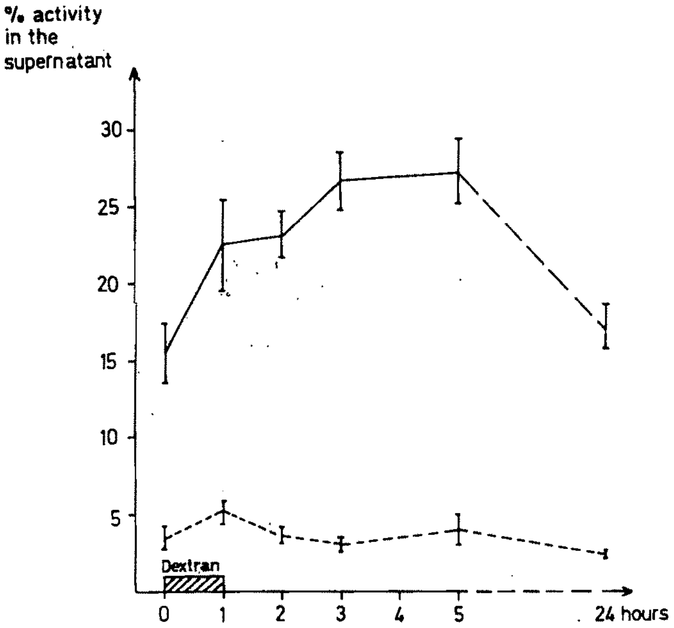

FIG. 1. Radioactivity in the supernatant as % of total activity after incubation with plasmin (——) or NaCl (– – –) before and after dextran infusion. Mean values and SE from 12 patients.

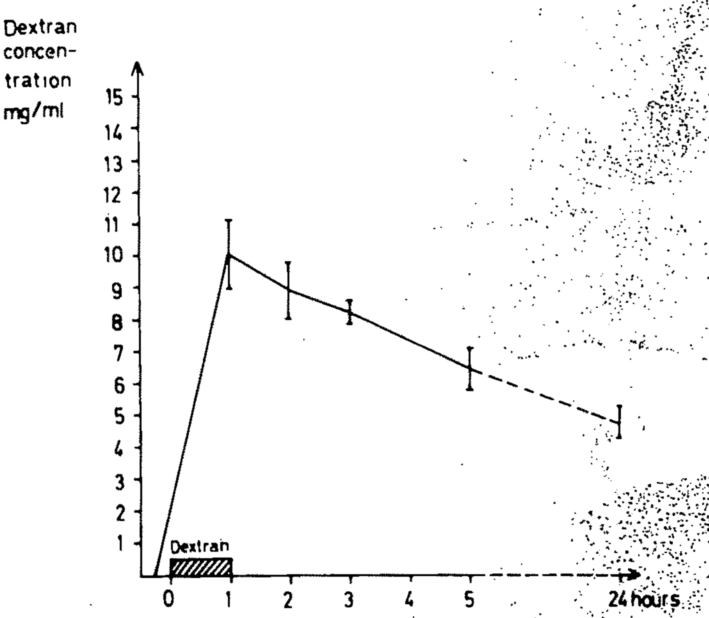

FIG. 3. Dextran concentration in plasma from patients receiving dextran infusion. Mean values and SD from seven patients.

patients labelled with ^{125}I-fibrinogen was withdrawn. After addition of dextran to a final plasma concentration of 0.5–10%, the blood was rotated in a Chandler loop. The thrombi formed during 1 hour were treated as described above. After the operation all patients were examined for thrombosis using an isotope localisation monitor.[17]

Results

In the patients receiving dextran the mean radioactivity in the supernatant after incubation with plasmin of the thrombi formed before dextran infusion was 15.5 ± 7.6% of the total activity (Fig. 1). Immediately after the infusion the activity increased to 22.7 ± 9.6% ($P<0.05$) and one hour later to 23.3 ± 5.9% ($P<0.01$). The maximal increase was obtained two hours after the end of the infusion (26.8 ± 7.1%, $P<0.001$). After four hours, the activity remained at the same level (27.3 ± 8.2%) and 24 hours after operation the activity had returned to the initial value (16.3 ± 5.2%). A corresponding rise of the FDP concentration in the supernatant from 16.8 µg/ml to a maximum of 44.1 µg/ml ($P<0.02$) at four hours after the end of the infusion was obtained.

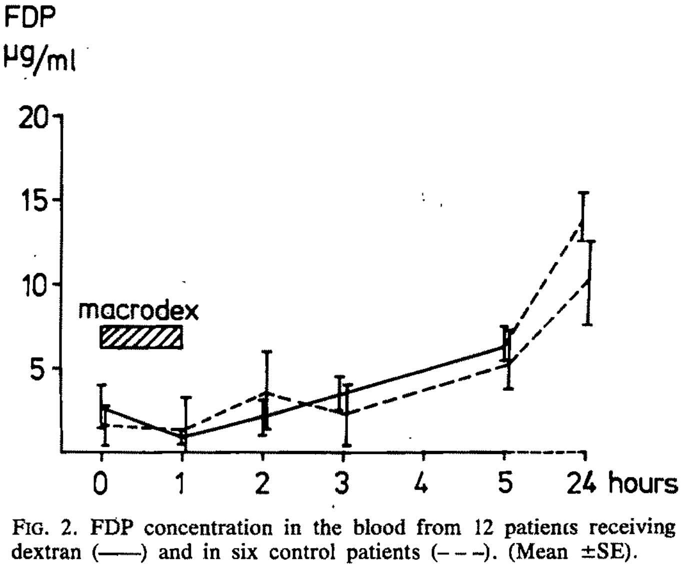

FIG. 2. FDP concentration in the blood from 12 patients receiving dextran (——) and in six control patients (– – –). (Mean ±SE).

If the thrombus was incubated in isotonic saline instead of plasmin, neither radioactivity nor FDP concentration in the supernatant increased (Fig. 1).

The FDP concentration in blood (Fig. 2) did not change during the infusion, but in the following four hours there was a successive increase from 0.8 to 6.3 µg/ml ($P<0.001$). The maximal FDP concentration in blood was found 24 hours after the end of the infusion (mean ± SD = 14.0 ± 5.1 µg/ml, $P<0.001$), followed in the next two days by a gradual decrease.

Factor XIII concentration did not vary significantly during and after the infusion neither in platelet-rich nor in platelet-poor plasma.

The dextran concentrations in plasma are shown in Fig. 3. The mean concentration was maximal at the end of infusion, (10.0 ± 1.0 mg/ml plasma) and then gradually decreased.

In control patients, not receiving dextran, there was no increased lysability after incubation of the thrombi with plasmin as indicated by the radioactivity in the supernatant (Fig. 4). There was no significant rise of the FDP in the supernatant. A moderate rise of FDP in the blood not

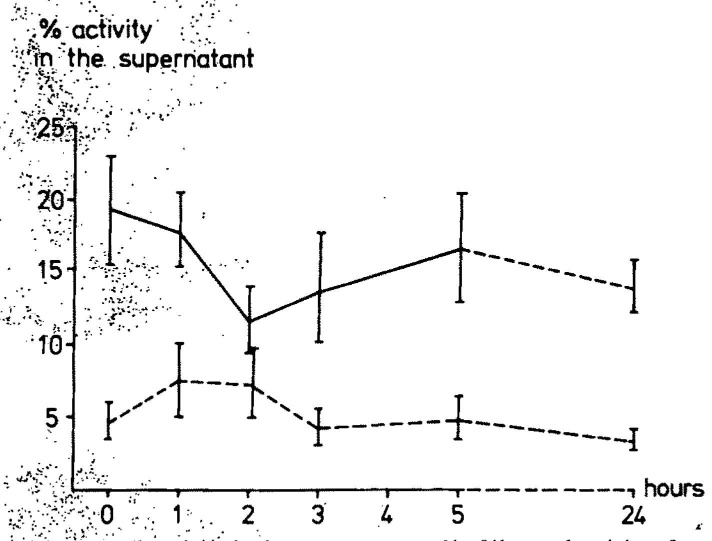

FIG. 4. Radioactivity in the supernatant as % of the total activity after incubation with plasmin (——) or NaCl (----). Mean values and SE from six control patients.

significantly different from that of patients receiving dextran was found (Fig. 2).

After addition of dextran in vitro to blood in increasing amounts to a final concentration of 100 mg/ml plasma, the radioactivity released into the supernatant rose from 12.8% to 46.3% (Fig. 5). When, however, the dextran concentration was 11 mg/ml plasma, roughly corresponding to the highest concentration obtained in vivo, the radioactivity increased only to 20.8% ($P>0.05$).

None of the dextran treated patients, but one of the control patients developed venous thrombosis in the legs as demonstrated by the ^{125}I-labelled fibrinogen test.

Discussion

The effect of dextran to decrease the incidence of postoperative thrombo-embolism is well established.[2,5,9,15,18] This effect has been demonstrated most convincingly if the dextran is given during the operation.[15] The antithrombotic effect has at least partly been ascribed to the decrease of platelet adhesiveness.[4,8]

Recently, however, some evidence has appeared indicating that the platelets do not play such a dominating role for development of venous thrombosis.[7,27] Another possible explanation for the antithrombotic properties of dextran may be its effect to improve the blood flow in the muscle veins of the lower legs during the operation.[15]

If the ^{125}I-fibrinogen test is used to diagnose thrombosis the antithrombotic effect of dextran is less obvious than if phlebography is performed later in the postoperative course. [3] This finding suggests an increased lysability of thrombi formed in the presence of dextran, which thus could contribute to the antithrombotic effect. Muzaffar et al.[23] found that dextran in vitro as well as in vivo changes the structure of the fibrin, resulting in fibrin fibres more variable in size and coarser than normal. In vitro studies have shown that such morphologically changed fibrin clots are more easily dissolved by plasmin.[29]

The increased lysability demonstrated in the present study was apparent as an increased activity of I^{125} in the supernatant. This is due to release of radioactively labelled split products, as previously demonstrated by Nordström and Zetterquist.[25] The amount of FDP in the supernatant after plasmin incubation rose parallel to the radioactivity confirming that the release of radioactivity

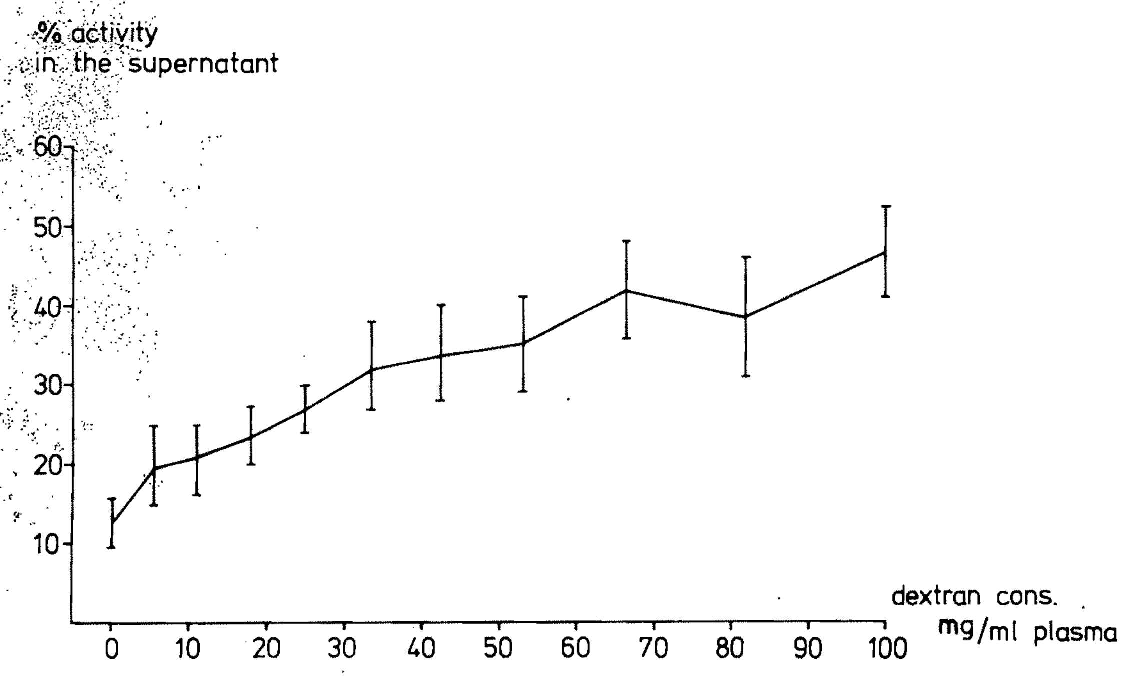

FIG. 5 Radioactivity in the supernatant as % of total activity after incubation of thrombi with plasmin. Dextran added in vitro. Mean values and SE from four patients.

from the thrombi really corresponds to a plasmin-digestion of the fibrin in the thrombi. The increased lysability was apparent already at the end of the dextran infusion, but reached a maximum about four hours after the end of the infusion. Thus the curve for increased lysability did not parallel the curve for dextran concentration. This finding agrees with the decrease of platelet adhesiveness after dextran infusion, which also reaches a maximum after four hours.[8,11] Some relationship between the effect of dextran on fibrin lysability and platelet function is therefore suggested. It has been shown by Paterson and Dhall[28] that infusion of dextran is followed by a transient platelet aggregation with release of ADP. Although the ADP content of the platelets is normalised within one hour after the end of the dextran infusion, releasable amount of ADP was decreased for many hours. When platelets aggregate, other substances such as antiplasmins, inhibitors of the plasminogen activation and factor XIII have been found to be released.[12,21,26,30] Factor XIII is known to initiate the cross-linking of fibrin fibers, thereby making the thrombi more stabile. Lack of factor XIII increases the lysability of thrombi. In the present study no evidence was found to indicate a decreased activity of factor XIII after dextran infusion.

When dextran was added in vitro the increased lysability was small as long as the dextran concentration was below 11 mg/ml plasma, which is the highest concentration obtained in vivo. The lysability increased with increasing dextran concentration, which is in agreement with the in vitro findings by Tangen et al.[29] When dextran was given to patients the maximal increase of lysability was found not at maximal dextran concentration but when this concentration had decreased to 6.4 mg/ml. Thus the increased lysability observed in the present ex vivo study is not related to the concentration of dextran, and probably due to some interaction between dextran and blood occuring in vivo, possibly via the platelets.

Dextran does not initiate general fibrinolysis.[11] The FDP found in the blood of the patients in this study was not caused by the dextran infusion, but by the operative procedure, as apparent from the finding of FDP also in the control patients.

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Spontaneous Reversal of Portal Blood Flow:

The Case For and Against Its Occurrence in Patients With Cirrhosis of the Liver

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Because of its presumed serious clinical significance, we made an analysis of the evidence for and against the occurrence of spontaneous reversal of portal flow in cirrhosis of the liver. We examined the evidence obtained from manometric studies, radioactive tracer studies, radiologic studies, and actual measurements of magnitude and direction of portal blood flow. Concerning manometric studies, we introduced a physical analysis, based on first principles, which demonstrates that the occluded portal pressures cannot be used to construct a hydraulic gradient for portal flow. Similarly, we examined the weakness of the evidence derived from radioactive tracer and radiologic studies and, in the latter, the drastically opposite results reported by different investigators. Finally, we found that actual measurements of magnitude and direction of portal flow provide impressive evidence against the occurrence of spontaneous reversal of portal flow in cirrhosis. We conclude that unless new and convincing evidence is provided, it may not serve the best interests of medicine and of our patients to continue accepting spontaneous reversal of portal flow in cirrhosis as if it were a proven phenomenon.

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SPONTANEOUS REVERSAL of portal flow implies that the portal vein delivers hepatic blood into the splanchnic bed instead of delivering splanchnic blood into the liver as intended in the orderly scheme of nature. This departure from the normal order has been predicated on the basis of the outflow tract obstruction prevailing in cirrhosis.[1,25,58] Under these conditions, the blood entering the liver through the hepatic artery would find it easier to exit the organ through the portal vein than through the normal route of the hepatic veins. The diverted hepatic blood would then fight its way against the incoming splanchnic flow and eventually reach the right heart via the collateral network.

Apparently, the need for a concept of spontaneous reversal of portal flow was created by some unexpected results observed after side-to-side portacaval anastomosis. At the time, it was becoming increasingly clear that this operation was not yielding the results originally predicted, i.e., decompression of the splanchnic bed and varices with preservation of some hepatic perfusion by portal blood. Quite the contrary, it was evident that while the lower limb of the shunt was effectively decompressing the splanchnic bed, its upper limb appeared to be draining hepatic blood into the inferior vena cava. The question immediately arose as to whether the hepatic arterial blood now leaving the liver through the shunt had had an opportunity to perfuse the hepatic cell or, if by taking the route of arterio-portal anastomoses, it had actually bypassed the sinusoidal bed. Primarily on the basis of measurements of hepatic oxygen consumption, two different camps of opinion were promptly formed.[28,37,38,44,54] In the meantime, the concept of spontaneous reversal of portal flow in cirrhosis proved to be a more convenient alternative for the dilemma. Here, the reasoning was that if a patient with advanced cirrhosis already had his portal flow spontaneously reversed before any surgical intervention, then the shunt would only complete the task initiated by nature,[57,58] and the matter of perfusion of the liver cell would become a moot question.

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At this writing, the concepts of outflow block in the formation of ascites advanced by Madden,[25] and of correcting this complication by simultaneous splanchnic and hepatic decompression pioneered by Welch[58] and McDermott,[26] appear to have become definitely established on their own merits. Therefore, it seems no longer necessary to advance hypothetical arguments to justify the rationale of the side to side shunt. Unfortunately, the hypothesis of spontaneous reversal of portal flow in cirrhosis[57] has survived on the basis of what, after all, may only be "circumstantial" evidence. Recently, the presence of alleged spontaneous reversal of portal flow has been reported to be associated with different mortality and morbidity after portacaval shunts performed during acute bleeding.[7] In this report we intend to examine in some detail the evidence available for and against spontaneous reversal of flow in the portal vein of patients with cirrhosis of the liver. For convenience, we will examine the evidence under four main subheadings: manometric studies, radioactive tracer studies, radiologic studies and actual measurements of magnitude and direction of portal flow.

Manometric Studies

Measurements of pressure on the hepatic and splanchnic sides of a clamp occluding the portal vein have been used in the literature to support the presence of spontaneous reversal of flow in the portal vein of patients with cirrhosis of the liver. If the pressure on the hepatic side of the clamp were higher than either the free portal pressures or the pressure on the splanchnic side of the clamp, the blood, flowing from the higher to the lower pressure, would leave the liver through the portal vein and enter the splanchnic circulation.

In the previous reasoning, the unstated but necessarily implied assumption is that the pressure on the hepatic side of the clamp approximates the pressure in the sinusoids of the liver and that this approximation holds not only during the portal occlusion but also when the portal blood is flowing into the liver. That being the case, the difference between the hepatic occluded and the free portal pressure would become a true pressure differential or hydraulic gradient for flow in the portal vein.[27] Similarly, the difference between hepatic and splanchnic occluded portal pressures would become some sort of potential gradient for flow which has been designated as the "maximum perfusion pressure."[54,56,57] These concepts have become ingrained so deeply in our routine clinical thinking that even surgical residents react with surprise, and sometimes with hidden or overt indignation, to any attempt to question their validity. Frequently, such questioning is taken with the connotation of a challenge to the fundamental laws of nature. And yet, it is simpler to demonstrate the physical weakness of these hemodynamic concepts than to trace the oversimplifications which, explicitly or implicitly, were used to introduce them as legitimate expressions of valid laws of physics. In the next paragraphs we will attempt to examine these oversimplifications and some of their natural consequences.

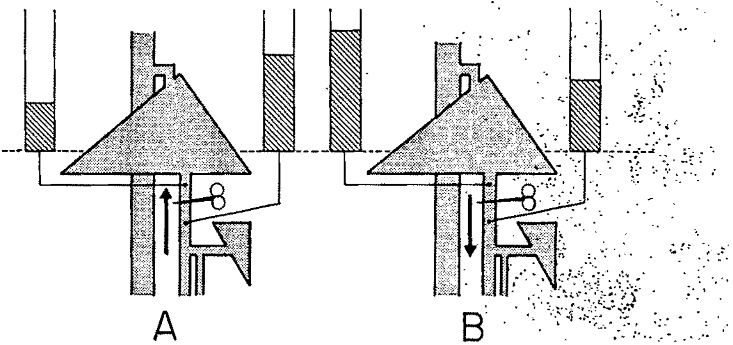


FIG. 1. Common interpretation of the significance of pressures measured on the hepatic and splanchnic sides of a clamp occluding the portal vein. (Redrawn after Conn[9]). A. When the pressure on the splanchnic side of the clamp (SOPP) is higher than the pressure on the hepatic side of the clamp (HOPP), the portal blood should flow into the liver in the normal fashion. Portal flow is then variously said to be forward, cephalad, hepatopetal, or antegrade. B. When the hepatic occluded pressure is higher than the splanchnic occluded pressure, the portal blood should flow out of the liver into the splanchnic bed. Now, the portal flow is said to be reversed, caudal, hepatofugal, or retrograde. (See Fig. 2 for a model that would be compatible with this interpretation.)

A good example of the current interpretation of the occluded portal pressures is given in Fig. 1 which has been redrawn from an illustration in a writing by Conn.[10] On the left side of Fig. 1, labelled A, two manometers are represented by reservoirs adjusted to a common datum plane given by the broken line. The level in the reservoir connected to the splanchnic side of a clamp occluding the portal vein is higher than the level in the reservoir connected to the hepatic side of the occluded portal vein. As the arrows near the portal vein indicate, the splanchnic blood should enter the liver in the normal manner. On the right side of the illustration (B), the level in the reservoir connected to the hepatic side of the occlusion is higher than that of the one connected to the splanchnic side of the occlusion. The arrow along the portal vein indicate that now the hepatic blood should flow out of the liver into the splanchnic bed. The apparent disarming logic of this reasoning can be immediately challenged. Although we have objected to the current abuse of the word "model" in medical writings,[35] we have nothing against its proper use and, therefore, will search for a model that would be compatible with the previous reasoning. Then, we will compare the model with reality to see if it can be considered an adequate representation of the true physical system under discussion.

Figure 2 shows a model compatible with the interpreta-

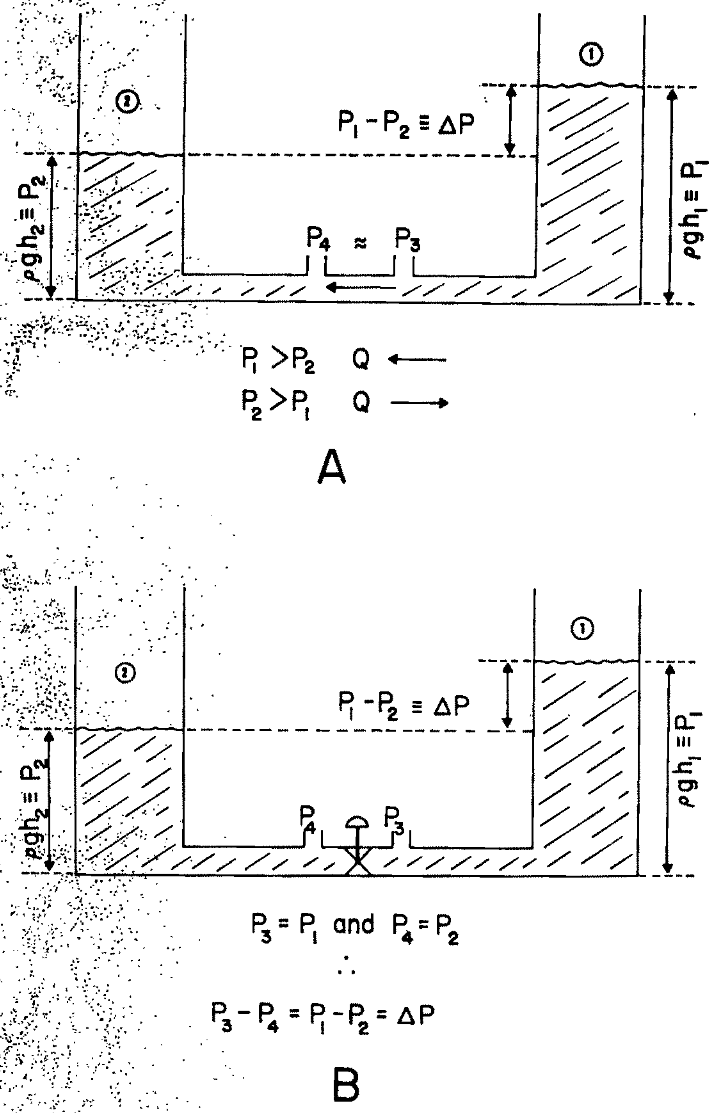


FIG. 2. A simplified model that would be compatible with the interpretation that the pressures on the hepatic and splanchnic sides of a clamp occluding the portal vein could be used to construct a hydraulic gradient for flow in the portal vein. A. Liquid flows from Reservoir 1 to Reservoir 2 through a smooth pipe of constant cross-sectional area. For constant density of the fluid (ρ) and consant acceleration of gravity (g), only the heights h_1 and h_2 determine the pressure in the reservoirs. The difference between these pressures is the hydraulic gradient for flow (ΔP). The direction of flow (Q), is a function of the relative magnitudes of P_1 and P_2. Pressures at two close points in the pipe (P_3 and P_4) are almost identical due to the short distance separating the points and to the absence of any narrowing or roughness of the pipe between them. Measurements at these points will not reflect the gradient for flow in the system. B. A valve has been closed between points 3 and 4 in the pipe and there is no flow in the system. If this model would be an adequate representation of the splanchnic-hepatic-collateral system in cirrhosis, closing of the valve would be equivalent to clamping the portal vein. Now points 3 and 4 are connected to their respective reservoirs by static columns of fluid and $P_3 = P_1$ while $P_4 = P_2$, then $(P_3 - P_4) = \Delta P$, the gradient for flow in the system. This model sustains the interpretation of the occluded portal pressures advanced in the literature (see Fig. 1). However, the model is not an adequate representation of the true physical system in cirrhosis. First, the model represents an open, gravity system and, second, the reservoirs do not have the outlets which in the real system are provided by the hepatic veins and the collateral network respectively.

tion of the occluded portal pressures given above. Essentially, the illustration shows two reservoirs (1 and 2) connected by a smooth pipe of constant cross-section. In Fig. 2A, flow is taking place from 1 to 2 on the basis that P_1 is greater than P_2. In this model, for fluids of constant density (ρ), submitted to a constant acceleration of gravity (g), only the height of the column of fluid (h) is required to define the pressure. The difference (P_1 - P_2) is the gradient for flow in the system (ΔP). With P_1 greater than P_2, the flow proceeds from 1 to 2 and ΔP is said to be positive. With P_2 greater than P_1, we have flow from 2 to 1, and ΔP is said to be negative. The difference between the pressure measured at two points closely located in the pipe (P_3 and P_4) is very small due to the proximity of the points and the absence of any narrowing of the pipe between them.

If one now occludes the pipe between the points where P_3 and P_4 are being measured, equivalent in this model to clamping of the portal vein, the points become connected to their respective reservoirs by static columns of fluid (Fig. 2B). These columns of fluid act as manometers or as extensions to any manometer connected to the points 3 and 4. Then, the difference between P_3 and P_4 would equal the difference between P_1 and P_2 and, therefore would equal the true gradient for flow in the system (ΔP). If this model adequately represents the splanchnic-hepatic-collateral system in cirrhosis, the difference between the occluded portal pressures would be a measure of the true gradient for flow in the system. However, as we will discuss later in more detail, the model does not represent the real system adequately, and we have the case of a correct analysis for a model which is not a correct representation of the real system. In other words, it is not the model but its selection that is incorrect in this scheme.

The model in Fig. 2 is not an adequate representation of the splanchnic-hepatic-collateral system in cirrhosis on two main counts: first, it represents an open, gravity flow system and, second, it does not provide for outlets to the reservoirs, i.e., hepatic veins outflow for the liver reservoir and collateral bed outlet for the splanchnic reservoir. If one would like to persist with the open gravity flow system and provide the necessary outlets for the reservoirs, one would obtain a model such as the one represented in Fig. 3. Here, the two reservoirs empty into a common third reservoir, the vena cava, by outlets which have a definite resistance. If we now occlude the pipe representing the portal vein between points 3 and 4, we note that P_3 and P_4 are no longer simple functions of the height of the levels of the reservoirs 1 and 2, but complicated functions of the pressure differentials between the various reservoirs, of the flow through the outlets, and of the resistance of the outlets. These relationships do not even include the pressure in the arterial reservoirs or the high arteriolar resistances which are

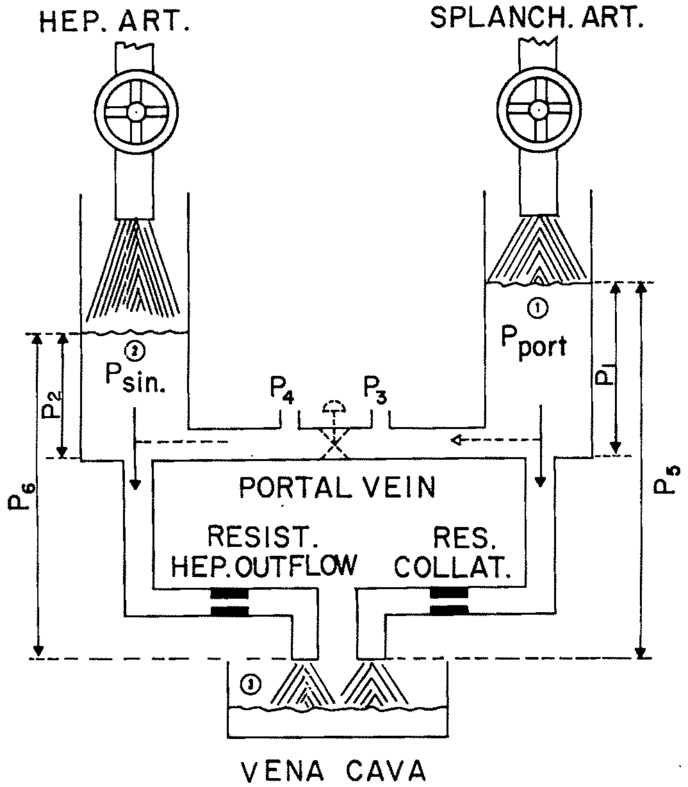
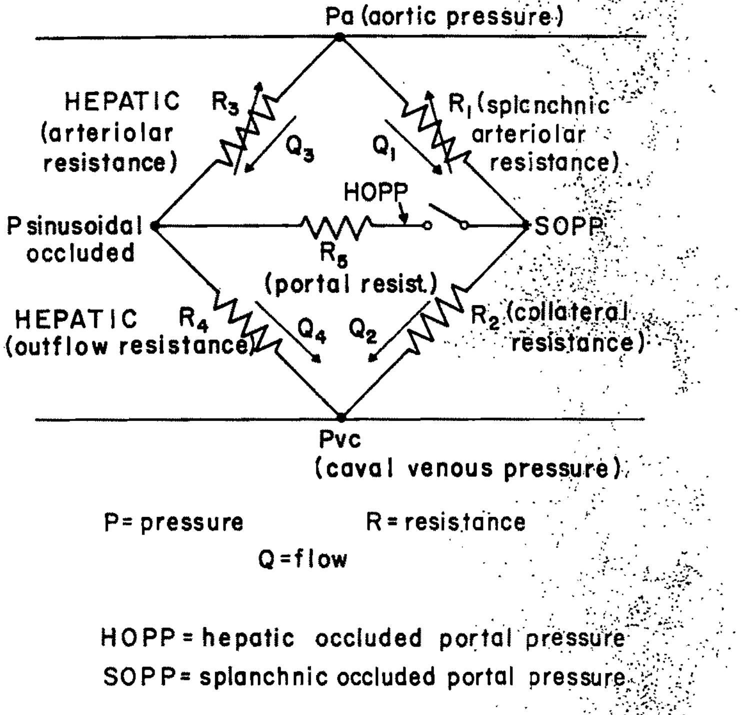


FIG. 3. A more realistic model of the splanchnic-hepatic-collateral system in cirrhosis. While still restricted by representing an open, gravity system, the model improves that shown in Fig. 2 by providing outflows to the reservoirs. The arterial inflows although shown refilling the reservoirs through high arteriolar resistances (heavy valves) will not be considered in a preliminary discussion. When the valve between points 3 and 4 in the pipe representing the portal vein is open, reservoir 1 (the splanchnic reservoir) divides its flow between the portal vein and the collateral outlet. In turn, reservoir 2 (the hepatic reservoir), empties the combined contributions of the hepatic artery and the portal vein into the vena cava through the resistance of the hepatic outflow. When the valve between points 3 and 4 is closed, flow through the transverse pipe (the portal vein) ceases but flow through the collateral and hepatic veins outlets continues. P_3 and P_4 are no longer simple functions of the height of the fluid in the reservoirs 1 and 2. Even disregarding the arterial pressure and the arteriolar resistances, P_3 and P_4 are still complex functions of the pressure differentials between the various reservoirs, of the outlet flows and of the resistance in these outlets (represented by black blocks). The arteriolar resistances, although not included in this discussion, are represented by adjustable valves to imply their ability for adjustments in short time scales. The hepatic outflow and collateral outlet resistances are represented by fixed resistances to indicate their capability for long term adjustments only. These adjustments may require months or even years as the cirrhotic process and the development of collaterals advance.


Pa (aortic pressure)
HEPATIC (arteriolar resistance) R3
Q3
Q1
R1 (splanchnic arteriolar resistance)
HOPP
P sinusoidal occluded
R5 (portal resist.)
SOPP
HEPATIC R4 (outflow resistance)
Q4
Q2
R2 (collateral resistance)
Pvc (caval venous pressure)
P = pressure
R = resistance
Q = flow
HOPP = hepatic occluded portal pressure
SOPP = splanchnic occluded portal pressure

$$\mathrm{HOPP} \approx P\mathrm{sin.\ occl.} = P\mathrm{vc} + (P\mathrm{a} - P\mathrm{vc})\, R_4/(R_4 + R_3) \qquad (1)$$

$$\mathrm{SOPP} = P\mathrm{vc} + (P\mathrm{a} - P\mathrm{vc})\, R_2/(R_2 + R_1) \qquad (2)$$

FIG. 4. The splanchnic-hepatic-collateral system in cirrhosis represented by the Wheatstone bridge analogy proposed by Bradley.[3] Clamping of the portal vein, represented by the open switch in the circuit, turns the bridge into two parallel circuits, i.e., the hepatic artery-hepatic veins circuit, and the splanchnic-collateral circuit. Equations 1 and 2 show the determinants for the hepatic occluded portal pressure (HOPP) and for the splanchnic occluded portal pressure (SOPP). Note that in Equations 1 and 2, the pressure terms are the same for both circuits and, therefore, that the difference is given by the resistive terms. These resistive terms are simply the ratio of the outflow to the total resistance on each circuit. The value of these ratios are the only determinants for the pressure on either side of the clamp to be higher or lower than the pressure on the other side. The important conclusion is that the hepatic occluded portal pressure (HOPP) approximates the sinusoidal pressure only when portal flow is not taking place. The value of the sinusoidal pressure when portal flow is taking place, the only value relevant for the construction of a hydraulic gradient for portal flow, is very different and is given by a much more complicated mathematical expression which we introduced in our reference.[36] As in Fig. 3, the arteriolar resistances are represented as variable resistances to indicate their ability for short time scale adjustments. Similarly, the hepatic outflow and hepatic outlet resistances are represented by fixed resistors to indicate their usual inability for short time scale adjustments.

represented in the sketch by heavy valves. Actually, at this point, it is no longer possible to carry further the analogy of the open, gravity system without introducing grave complications. Therefore, we will resort to a more manageable electric analogy using the Wheatstone bridge model proposed by Bradley.[3]

If one restricts the analysis to steady flows, leaving apart considerations of inertances and variable compliances, it is possible to apply directly the equations for the bridge developed in the field of electrical engineering.[14] In a previous communication,[36] we introduced such analysis for the splanchnic-hepatic-collateral system in cirrhosis (Fig. 4). As a result, we showed that the conditions for the pressure on either side of the clamp to be higher or lower than that on the other side are independent of the magnitude and direction of the portal flow and are determined uniquely by the ratio of the outflow to the total resistance on each of two parallel circuits, i.e., the hepatic artery-hepatic veins system on one side (Equation 1 in Fig. 4) and the splanchnic-collateral system on the other (Equation 2 in Fig. 4). These circuits have been made independent parallel circuits by clamping of the portal vein which removes the direct connection between them. The analysis also showed that when flow in the portal vein is not interrupted by a clamp, the conditions determining the free portal pressure and the unoccluded sinusoidal pressure are given by mathematical relationships drastically different from those determining the occluded pressures. Therefore, the sinusoidal pressure during occlusion is very different from the sinusoidal pressure during flow, a fact that precludes the use of the occluded pressures to construct a gradient for portal flow. This explains the clinical findings in two of our previous reports[6,36] where we found a complete lack of correlation between the differences in occluded pressures and the magnitude and direction of the portal flow in a series of 80 patients having all the necessary measurements. Actually, nine of these patients did have an hepatic occluded pressure which was higher than the free portal pressure or than the splanchnic occluded pressure. However, none of them had reversal of portal flow as assessed by direct measurements with the electromagnetic flowmeter. Two of these patients had stagnant flow and the remaining seven had forward flow into the liver measuring from 80 to 1116 ml/min. We will return to discuss the value of measurements with the electromagnetic flowmeter in the last section of this report.

In view of the discussion above, the findings recently reported by Charters et al.[7] remain in need of an explanation. These authors reported clinical correlations with the values of the occluded pressures and the presumed direction of the portal flow in patients operated during acute bleeding. However, from a purely statistical frame of reference, their conclusions seem difficult to justify. When they state that encephalopathy on admission was more common in patients with presumed reversal of flow, they give an incidence of 27% versus 17% in patients with presumed forward flow. If a contingency table is prepared according to the statistical makeup of the group, a test of significance renders a value of $\chi^2 = 1.822$ which for one degree of freedom yields the nonsignificant value of $P < 0.32$. Similarly, the difference in survival was not significant at the 5 per cent level ($P < 0.08$). Finally, the incidence of encephalopathy in the survivors, given as 23% for the patients with presumed reversal of flow versus 12% in those with presumed forward flow is statistically not significant ($\chi^2 = 0.108$ and no value of P can be computed). In reality, the data of Charters et al. show that their division of clinical results into patients having presumed reversed portal flow and into patients having presumed forward portal flow is hardly justifiable because a separation based on random selection would have a high probability of yielding the same results. In other words, both groups might have been extracted from a common group.*

Irrespective of the lack of correlation between the values of the occluded portal pressures and the magnitude and direction of the actual portal flow, the fact remains that Charters et al. did find a higher incidence of reversed pressure differences in their acutely bleeding patients. Without access to their raw data, one may only speculate that a sudden decrease in the outflow collateral resistance may have rendered a transiently higher incidence of reversed pressures. Such a decrease in collateral resistance may have resulted from the opening of a wide rent, at the site of bleeding, in the collateral circuit. In turn, this decreased in collateral outflow resistance may have lowered temporarily the resistive ratio in Equation 2.

The fact that the values of the differences between the occluded sinusoidal and splanchnic pressures do not determine the magnitude or direction of the portal flow should not be taken as a statement that true spontaneous reversal of flow cannot occur in this vessel. Using the Wheatstone bridge analogy one can derive the conditions for the unoccluded sinusoidal pressure to exceed the portal pressure. Essentially, these conditions require a much larger hepatic outflow resistance than the resistance in the collateral bed. Since the difference between the unoccluded sinusoidal and the free portal pressure is a true pressure differential or hydraulic gradient for flow, there would be spontaneous reversal of portal flow whenever the unoccluded sinusoidal pressure exceeds the free portal pressure. This condition must not have existed in any of the patients in our study. Apparently, the value of the hepatic outflow resistance was not sufficiently large in our patients with cirrhosis to produce spontaneous reversal of portal flow. Conversely, its value should be very large in Budd-Chiari syndrome with almost complete obstruction of the outflow tract. This might be the reason why true spontaneous reversal of portal flow appears to occur in this syndrome.[16,40,43,47]

On the basis of our analysis and clinical measurements, we conclude that there is no justification for the claims of spontaneous reversal of portal flow in cirrhosis reported in the literature if the claims are based solely on the presence of an hepatic occluded portal pressure which is higher than either the free portal or occluded splanchnic pressure.

Radioactive Tracer Studies

The studies of Longmire et al.[24] in 1958, are often quoted in the literature as proof of spontaneous reversal of portal flow in cirrhosis. Careful reexamination of the protocol of the studies shows, once more, that the evidence for spontaneous reversal might be more "circumstantial" than definitive.

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*For the case of the incidence of encephalopathy in the survivors, the use of the χ^2 statistics may be questioned because there is an expected frequency lower than five. However, any attempt of correction, for example the Yates correction, makes the results even less significant.

These authors inserted catheters in the splanchnic-hepatic system of patients about to undergo side to side portacaval shunts. One catheter was located in a peripheral mesenteric vein, another was advanced into the main trunk of the portal vein well cephalad to the site of the intended anastomosis, and a third catheter was threaded into the hepatic artery through one of its branches. Injecting radioactive tracer into the peripheral mesenteric vein and sampling from the cephalad catheter in the portal vein, they detected the passage of a large bolus of radioactivity. This was interpreted as forward portal flow carrying the peripherally injected tracer into the liver. However, injecting into the hepatic artery and sampling, again, from the cephalad portal vein, the authors noted that some radioactivity "may be immediately detected" in the portal blood. This time the interpretation was that some backflow of hepatic arterial blood into the portal vein may have been taking place. Now, these interpretations are mutually exclusive, i.e., the first injection shows forward flow while the second injection shows reversed flow. It might be argued that in living systems there are occasions where diffusion of substances do occur against hydraulic, chemical or electrical gradients. However, this requires mechanisms of active transport with elaborate use of energy. Such is the case of the transport of ionic calcium into the sarcoplasmic reticulum during muscular relaxation. Here, the transport is achieved against a gradient of concentration through the energy yielding splitting of ATP.[23] An equivalent process is described by the formalism of the thermodynamics of irreversible processes as "incongruent" diffusion.[17,42] There are many "pumps" of this sort operating in living beings, but few would claim such sophisticated mechanisms to explain the diffusion of a modest radioactive tracer against the incoming portal flow. A simpler explanation could be that the suction exerted by the cephalad catheter resulted in some sampling of sinusoidal blood rightly containing isotope. This is conceivable if one compares the order of magnitude of the suction created by a sampling syringe with that of the small pressures prevailing in the portal-sinusoidal system. In a group of 23 patients with cirrhosis, Reynolds compared the values of the sinusoidal pressure using hepatic vein wedged measurements and of the portal pressure measured simultaneously through the recanalized umbilical vein.[45] He found that the sinusoidal and portal pressures were almost identical, a fact that shows the very small resistance existing between the portal vein and the sinusoids.

After constructing the side to side shunt, Longmire and associates repeated their series of injections. The results were now reversed, i.e., the portal cephalad samples showed little or no radioactivity after mesenteric peripheral injection and large radioactivity after hepatic arterial injection. The radioactivity after hepatic arterial injection was measured as several times larger than that detected before constructing the portacaval shunt. The probably correct interpretation was that now the mesenteric blood was diverted into the vena cava through the lower limb of the shunt while the upper limb, acting as an accessory outflow tract, was carrying hepatic blood away from the liver.

The results of the important studies of Longmire and associates indicate that reversal of flow does take place in the hepatic limb of a side to side portacaval shunt. However, it is highly improbable that they could be construed as proof of spontaneous reversal of portal flow in cirrhosis.

Radiologic Studies

Five primary radiologic methods have been used to attempt a demonstration of spontaneous reversal of flow in the portal vein of patients with cirrhosis: 1) retrograde injection of contrast medium from the "wedged" hepatic vein position; 2) portal injection through catheterization of the umbilical vein; 3) splenic portography; 4) selective hepatic arteriography; and 5) hepatic intraparenchymal deposition of contrast medium.

Retrograde Injection of Contrast Medium from the Wedged Hepatic Vein Position

Warren et al.[55–57] and Viamonte et al.[53] have most persistently reported the occurrence of spontaneous reversal of portal flow in cirrhosis on the basis of their observations following hepatic vein "wedged" injection of contrast material. In this technic, the opaque medium is introduced under pressure through a catheter wedged into a small hepatic vein branch and forced, in retrograde fashion, into the sinusoids and the portal venules. According to these authors, more advanced degrees of cirrhosis with smaller portal blood inflow would facilitate the retrograde injection and the visualization of the portal branches. If the main trunk of the portal vein is visualized, the flow in this vessel is said to be retrograde, i.e., the portal blood would be flowing out of the liver into the splanchnic bed. Visualization of the coronary system and varices would further affirm the presumption of spontaneous reversal of portal blood flow. Conversely, it would be very difficult to force contrast material into the portal vein system of normal subjects having large portal inflows.

Opposite findings have been reported by Ney[39] who showed that the contrast medium could be forced into the main portal vein of normal subjects, by Britton[4] who found that very little pressure is required to force contrast material into the portal trunk of most patients with cirrhosis, and by Smith[49] who found a greater incidence of this forced retrograde filling of the portal system in patients with early cirrhosis. Perhaps the report of Smith et al. contains the most damaging evidence against the ability of these forced, retrograde injections to demonstrate, without artifacts, the presence of spontaneous reversal of portal blood flow. Their communication includes a patient who showed what was considered a most typical pattern of presumed spontaneous reversal of portal flow during the wedged hepatic vein injection and who, at operation, was found to have a forward flow of 480 ml/min as measured by the electromagnetic flowmeter. In our own studies,[46] we found a patient with such extensive retrograde filling of the portal system after hepatic vein wedged injection, that true spontaneous reversal of portal flow in cirrhosis appeared to have been confirmed. However, during measurements with the electromagnetic flowmeter, the patient was found to have forward portal flow into the liver measuring 165 milliliters per minute. Finally, Smith et al, also studied 11 patients after side to side portacaval anastomosis. Despite the fact that most of these patients are known to have reversal of flow in the hepatic limb of the shunt, none of them showed evidence of such reversal during hepatic vein wedged injections.

The conflicting findings reported by different authors, occasionally being one hundred and eighty degrees out of phase, cast serious doubts on the occurrence of spontaneous reversal of portal flow in cirrhosis when only evidence from hepatic vein wedged injection is brought in its support. The conflicting findings should not be unexpected in a method which is based on the retrograde injection of contrast. If the material is forcefully backed up to the level of the junction with the coronary vein, at the point where the splanchnic flow divides between the portal vein and the collateral bed, the medium would easily take the route of gastroesophageal varices and this needs not imply that the portal flow had spontaneously reversed its direction in the absence of the forced injection.

Even accepting the reports of Warren and associates as proof of the validity of the hypothesis of spontaneous reversal of portal flow in cirrhosis, the evidence would still be sparse. We had difficulties keeping our arithmetic straight while sorting out the patients repeatedly included in their various reports. Within these difficulties, we were able to identify only six patients having presumed reversal of portal flow in the reports published between 1963 and the present writing.

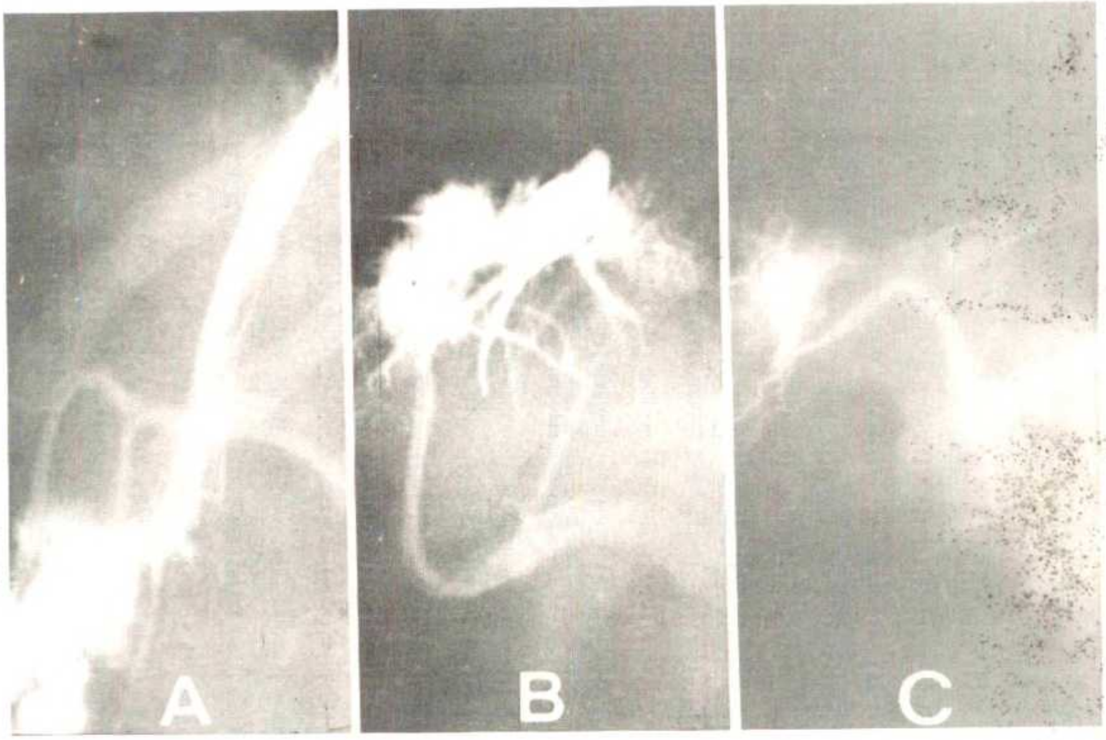
Portal Injection Through Catheterization of the Umbilical Vein

Kessler and associates[18] have reported on this method. They catheterized the umbilical vein and injected 40 ml of 75% contrast material at 125 psi. This is followed by complete flooding of the portal vein and varices. However, when the injection ceases and the portal inflo resumes, the dye stained portal blood is observed t perfuse the liver in the normal manner. They also note that in some patients the flooding was more intense an was not followed by the forward hepatic perfusion wit radiopaque portal blood. They interpreted these finding as indicating the presence of spontaneous reversal portal flow which prevented the entrance into the liver the radiopaque blood. Although this explanation is plau ible, an equally convincing case could be made for thes patients having stagnant flows, a condition that we hav reported to occur in eight per cent of portal flow mea urements in patients with cirrhosis.[6,32,36]

At any rate, the technique of flooding the portal vei devised by Kessler et al. has shown the lack of hepati perfusion that could be interpreted as indicating spo taneous reversal of portal flow in only two patients wit cirrhosis in a series of 150 examined by them. In a late report,[19] they have increased the number of patients wit cirrhosis studied by this method to 232 patients. The also added refinements of the technic which should lea to a better demonstration of spontaneous reversal portal flow in these patients. However, they do n include any new patients with this condition in this late report.

Splenic Portography

During the early experience with this method, lack visualization of the portal vein was interpreted as t result of either anatomic obstruction of the portal vein of spontaneous reversal of portal blood flow. In the ca of the presumed reversal of flow, the blood exiting t liver through the portal vein would prevent the contra material from entering the vessel and outlining its co tour.[20] Increasing use of splenic portography, which our group surpassed the 1000 patient mark before bei partially replaced by selective arteriography, showe that most cases of non-visualized portal vein were a sociated with an anatomically patent vessel. Moreove no reversal of flow could be found in the patent vessel We have devoted an entire report to the examination this problem,[5] and have evaluated the lack of justificati for making a diagnosis of spontaneous reversal of port flow based on non-visualization of this vessel duri splenic portography. In that report we included dire measurements of portal flow in 14 patients with cirrhos and non-visualized portal vein during splenic porto raphy. Three of these patients had stagnant flow whi the remaining 11 had forward flows averaging 400 ± 3 (S.D.) ml/min. More recently, we have retabulated o data and provided guiding diagrams of the hemodynam patterns associated with non-visualization of the port vein during splenic portography.[46] However, the possib ity of associating non-visualization with spontaneo reversal of portal flow is revived from time to time a



IG. 5. Intraparenchymal eposition of contrast edium into the liver of hree patients with cirhosis submitted to side to ide portacaval shunt. A. n this patient, the pool of ontrast material is drained y a large hepatic vein and y the hepatic limb of the ide to side shunt acting as n accessory outflow tract. . In this patient the hepaic limb of the shunt apears to have become the rimary outflow tract. C. s in B, the hepatic limb of he shunt takes a primary ole as an outflow tract for he liver.

eintroduced as an accepted truth.[15] Had it not been for hese periodic revivals, this section would have been mitted in the present report.

elective Hepatic Arteriography

This is, perhaps, the most physiological method to ssess the presence of a suspected spontaneous reversal f portal blood flow. The contrast material is injected into he hepatic artery. The hepatic arteriolar resistance dissipates the arterial pressure in the normal fashion and lso dissipates any excess pressure resulting from the njection of the medium. The dye stained hepatic arterial lood perfuses the sinusoids and is collected by the utflow system, normally the hepatic venules and veins. n case of reversal of portal flow, the portal venules, the ortal veins and even the main portal trunk would be emoving the dye from the sinusoids. Boijsen and Ekman[2] have demonstrated this to be the case after splenorenal shunt. In their patient, the contrast medium inected into the hepatic artery escaped the liver through he portal vein, traversed the splenic vein and emptied hrough the shunt into the systemic circulation. In our wn studies using hepatic arteriography,[46] we have seen his reversal of flow to take place in the hepatic limb of a ide to side portacaval shunt.

Selective hepatic arteriography has also shown spontaneous reversal of portal blood flow in patients with Budd-Chiari syndrome. Pollard and Nebesar[40] observed the contrast injected into the hepatic artery to exit the liver via the portal vein in two patients with bilateral obstruction of the outflow tract. They also observed retrograde flow in one lobe obstructed by veno-occlusive disease into the portal branch of the normal lobe. There, the forward direction of flow was resumed. Ruzicka and Rossi[47] also reported reversal of portal flow after hepatic artery injection in one patient with Budd-Chiari syndrome.

Hepatic artery selective angiography has about the best opportunity to show reversal of portal flow, either following some type of side to side shunt or, spontaneously, in association with bilateral or unilateral veno-occlusive disease. Considering the extensive use of this method, it is remarkable that there are no reports, to our knowledge, indicating spontaneous reversal of portal flow in cirrhosis. Pollard and Nebesar[40] go as far as to state that, except for veno-occlusive disease, they have never seen spontaneous reversal of portal flow in any conditions studied by them in 30 patients.

Intraparenchymal Hepatic Deposition of Contrast Medium

In 1963[31] we introduced the clinical use of the intraparenchymal deposition of contrast medium in the liver of patients with hepatic cirrhosis. This clinical application was preceded by extensive experimentation in small[29] and large[30] laboratory animals. At the time, we were searching for more physiological methods of studying the altered hemodynamics of patients with hepatic cirrhosis. Three somewhat unexpected results emerged from the clinical application of this method: 1) the visualization of the efferent lymphatic system of the liver in patients with cirrhosis and ascites; 2) the visualization of the hepatic limb of a side to side shunt acting as an accessory outflow tract; and 3) the recognition by others (16) that the method was the "only truly diagnostic study" for Budd-Chiari syndrome.

The capability of the method of intraparenchymal deposition of contrast medium to demonstrate retrograde flow in the hepatic limb of a side to side portacaval shunt is shown by the radiographs of the three patients grouped in Fig. 5. The plate corresponding to the first patient (A) shows how a pool of contrast material is formed in the parenchyma of the liver and how this pool is drained by hepatic venules into large hepatic veins and by portal venules into the hepatic limb of the shunt and into the vena cava. Figure 5B shows another patient in whom the hepatic limb of a side to side shunt acts as an outflow tract for the liver, and Fig. 5C shows similar findings in another patient.

In Budd-Chiari syndrome, bilateral or unilateral, intraparenchymal deposition has shown either total backflow into the splanchnic bed or partial retrograde flow into the healthy lobe.[8,16,43,44]

In addition to our original report,[31] we have further increased the number of our observations[34] which at present number 184 patients with cirrhosis and portal hypertension.[46] In this rather large series of patients with cirrhosis submitted to intraparenchymal deposition of contrast material, we have not found a single instance of spontaneous reversal of portal blood flow. The report of Ramsey and Britton[43] on 15 additional patients does not include any cases of spontaneous reversal of portal flow, and none is found in the reports of the English[8,9] or French[21] investigators who used intraparenchymal deposition of contrast as a method of investigation. Nevertheless, the method is not free of false positive results. In one of our patients with cirrhosis (see Fig. 7 in our reference 5), the intraparenchymal deposition forced contrast medium back into the main portal vein and mesenteric bed, thus simulating the occurrence of spontaneous reversal of portal flow. On high speed motion pictures taken on the same patient, it was shown that when the injection of contrast medium ceased, portal flow resumed its normal direction and the dye stained portal blood perfused the liver. At operation, measurements with the electromagnetic flowmeter indicated that the patient had a forward portal flow into the liver measuring 90 ml/min (see flow recordings also in Fig. 7 of our reference 5). Price et al.[41] in an article devoted mainly

TABLE 1. *Magnitude and Direction of Portal Blood Flow Measured by Various Methods in 273 Patients with Hepatic Cirrhosis and in 21 Normal Control Subjects*

		Electromagnetic Flowmeter					
		Patients with Cirrhosis		Normal Controls		Post Side to Side Shunt	
Authors	Year	Forward Flow	Reversed Flow	Forward Flow	Reversed Flow	Forward Flow	Reversed Flow
Schenk, McDonald, and Drapanas[47]	1962	5	-	9	-	-	-
Ferguson[12]	1963	11	-	-	-	-	-
Moreno, Burchell, Rousselot, *et al.*[31]	1967	85†	-	6	-	4*	9
Price, Vorhees and Britton[40]	1967	21	-	-	-	-	2
Fauvert[11]	1967	52	-	-	-	-	-
Leger, Lenriot, Gorin and Lemaigre[20]	1970	9	-	-	-	-	-
Smith[49]	1973	18	-	-	-	-	-
Burchell, Moreno, Panke and Nealon[6]	1974	145†	-	-	-	-	-
Moreno, Burchell, Reddy, *et al.*[35]	1974	153†	-	-	-	-	-
Subtotals		269	-	15	-	4*	11
		Electromagnetic Velocity Probe					
Strandell, Delin, Erwald, *et al.*[51]	1973	1	-	-	-	-	-
		Computer Analysis of High Speed Cineangiography					
Sovak, Soulen and Reichle[50]	1971	3	-	6	-	-	-
Grand Totals		273	-	21	-	4*	11

*Small magnitude.
†Cumulative series.

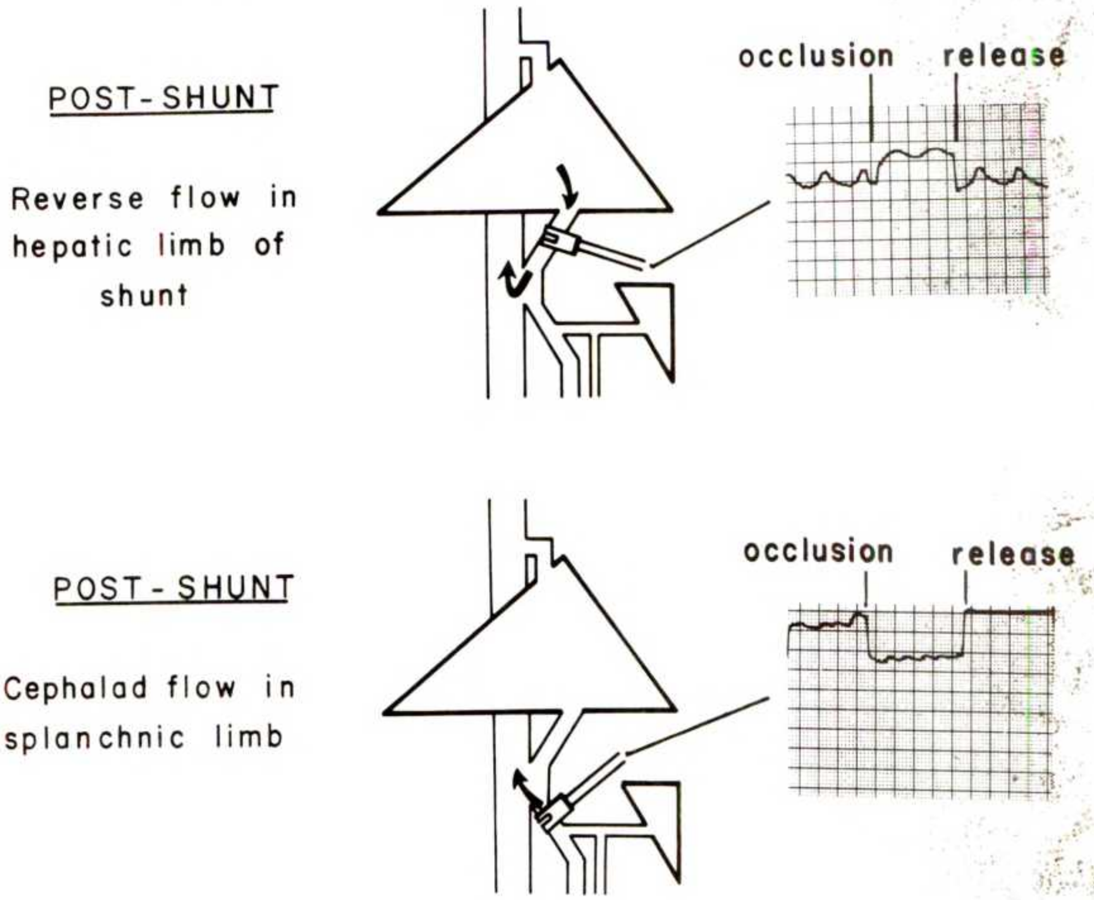

POST-SHUNT
Reverse flow in hepatic limb of shunt
occlusion
release
POST-SHUNT
Cephalad flow in splanchnic limb
occlusion
release

FIG. 6. Recordings with the electromagnetic flowmeter in one patient with cirrhosis after completing a side to side portacaval shunt. Note the ability of the flowmeter to measure retrograde or reversed flow in the hepatic limb of the shunt and forward or cephalad flow in the splanchnic limb.

to electromagnetic flowmeter studies, reported one patient with cirrhosis apparently showing spontaneous reversal of portal flow during intraparenchymal injection. Unfortunately, the authors did not provide electromagnetic flowmeter measurements in this uniquely interesting patient.

Actual Measurements of Magnitude and Direction of Portal Vein Flow

In a rather extensive review of the literature which includes the 12 year period between 1962 and the present writing, we have been able to collect measurements of magnitude and direction of portal flow in 294 human subjects. Of these subjects, 273 were patients with cirrhosis of the liver and portal hypertension and 21 were normal control subjects (Table 1). There was no single instance of measured spontaneous reversal of flow in the portal vein, although such reversal of flow was detected and measured in the hepatic limb of a side to side portacaval shunt in 11 patients.

Electromagnetic flowmeters, most frequently of the square wave type of Denison and Spencer,[11] were used in 284 subjects including 269 patients with cirrhosis and 15 normal control subjects. These flowmeters detected reversed flow very clearly when such reversal was present, i.e., after side to side portacaval shunt. Figure 6 shows tracings of flow obtained with one such instrument. After a side to side portacaval shunt, flow takes place in the retrograde direction in the hepatic limb of the shunt and in the forward direction in the splanchnic limb. Note the clear upward and downward deflection from zero line in the case of forward and retrograde flow respectively. At this point, we would like to correct an error frequently made when quoting the article by Price et al.[41] on measurements using flowmeters. The article is quoted as reporting three patients with spontaneous reversal of portal flow in cirrhosis. Actually, in two of the patients, the reversed flow was measured after side to side portacaval shunt, and did not occur spontaneously. In the remaining case, spontaneous reversal of portal flow was diagnosed by the method of intraparenchymal deposition of contrast medium and was not measured with the flowmeter. We have referred to this patient before in the section of radiologic studies.

Before concluding the discussion of measurements of magnitude and direction of portal vein flow using electromagnetic flowmeter, it is only fair to point out that in the report of Smith et al.[49] there is mention of one patient with cirrhosis who appeared to have spontaneous reversal of portal flow as detected by the electromagnetic flowmeter. Unfortunately, the authors did not measure, or did not report, the magnitude of such flow. This patient appears not to have been included in a later report by Smith.[50]

We have found only one report on the use of an electromagnetic velocity probe in the portal vein of a patient with cirrhosis,[52] and we include this patient as showing no spontaneous reversal of portal flow as measured by a slightly different technic. However, the truly independent measurements that could be taken as a guideline for comparison of the electromagnetic flowmeter are those reported by Sovak and associates.[51] These authors used a highly sophisticated technic which allowed them to measure portal flow in awake patients. This point is crucial, because of the frequent questioning of the validity of portal flow measurements at operation, with patients under anesthesia. After recannulating the umbilical vein several days prior to the measurements, Sovak and associates injected droplets of oily contrast medium at the hilum of the spleen. As the droplets traversed the splenic and portal veins, high speed cineangiograms were taken. The film was projected on a Thompson plotting table connected "on line" with a Linc Eight digital computer. A polynomial curve, derived from experiments in hydraulic models, was used to relate the droplet velocity to the true blood velocity.

With the careful technique just described, and with accurate biplane assessment of the cross-sectional area of the portal vein, Sovak and associates measured portal blood flow in six normal control subjects and obtained a mean value of 1160 ± 243 (S.D.) ml/min. This value and its standard deviation are of the same order of magnitude as our measurements with the electromagnetic flowmeter in normal subjects: 1299 ± 246 (S.D.).[32] What is more remarkable, they found respiratory oscillations amounting to 20% of the total normal flow, which is exactly the amount we reported with the electromagnetic flowmeter.[32] During inspiration they found that the velocity of the portal flow decreased to 5 cm/sec while during expiration the flow accelerated to 26 cm/sec. It was precisely this type of alternation which led us to formulate our early, two-chamber, hepatic valve model of respiratory regulation of systemic and splanchnic venous return.[33] Finally, Sovak et al. found further confirmation of our findings in cirrhosis. In their patients with this disease, the respiratory oscillations grew to become a substantial portion of the total flow. We had reported these oscillations to reach 40, 50, 80 and even 100% of the total flow in cirrhosis. The latter amounts we found in patients with stagnant flow showing only to and fro oscillations synchronous with the respiratory cycle. The Sovak et al. counterparts for these extreme cases were one patient in whom forward flow took place only during inspiration, and another patient, who showed only to and fro motions synchronous with respiration.

The unusually close agreement between two completely different methods of measuring portal vein flow, i.e., electromagnetic flowmeter measurements during anesthesia and computer analysis of high speed cineangiography in awake patients, increases our confidence in our findings, and in those of others using flowmeters, who failed to demonstrate spontaneous reversal of portal flow in cirrhosis.

Discussion

In a rather extensive review of the literature, we have collected most of the evidence that could be mustered to build a case for the occurrence of spontaneous reversal of portal flow in patients with cirrhosis of the liver. We have examined such evidence under four different headings: manometric studies, radioactive tracer studies, radiologic studies and actual measurements of magnitude and direction of portal blood flow.

The manometric evidence, as presented, has only the value of indirect evidence which requires accepting the assumption that the differences in pressure between the hepatic and splanchnic sides of a clamp occluding the portal vein, or between the hepatic occluded and the free portal pressure, are true pressure differentials or hydraulic gradients for portal flow. The lack of correlation between these differences in pressures and the measured portal flow, were the first signs of alert that these differences, after all, may not be true gradients for flow in the portal vein. The further demonstration that hepatic occluded pressures higher than the splanchnic occluded or the free portal pressure, can still coexist with significant forward portal flows added more doubts to the validity of the fundamental assumptions used to support the argument of the occluded portal pressures. We have been able to demonstrate by a theoretical analysis based on first principles, and by clinical measurements, that the hepatic occluded pressure approximates the sinusoidal pressure only during occlusion of the portal vein, but that it is quite different from the sinusoidal pressure in the absence of occlusion of the portal vein. Since the latter is the relevant quantity to construct a gradient for portal flow, the argument for using the hepatic occluded pressure becomes considerably weakened. Furthermore, reports in the literature correlating these differences with clinical results, are difficult to reconcile with simple statistical treatments.

Evidence from radioactive tracers studies make a good case for reversal of flow in the hepatic limb of a side to side portacaval shunt, but provides little if any evidence of spontaneous reversal of portal flow in cirrhosis.

Forced retrograde injection of contrast material into the portal system performed from the wedged hepatic vein position, has been proposed as proof of spontaneous reversal of portal flow in cirrhosis. Different investigators have reported completely opposite results. There are at least two patients in the literature who showed what was considered evidence of spontaneous reversal of portal flow during forced wedged hepatic vein injection but who were demonstrated to have significant forward flow during measurements with the electromagnetic flowmeter. Even accepting the validity of the findings of the most decided advocates of the technic of wedged hepatic vein injection, we have been able to find in their reports only six patients with presumed reversal of portal flow in cirrhosis during the period between 1962 and this writing.

Flooding of the portal vein with contrast material injected through the recannalized umbilical vein is normally followed by a washout which ends in hepatic perfusion by the dye stained portal blood. If this does not occur, the presumption of spontaneous reversal of portal blood flow is commonly advanced. Besides the fact that stagnant portal flow, which is found in 8% of patients with cirrhosis, would render the same results, the incidence of this presumed reversal of portal flow has been reported in only two patients with cirrhosis.

Non-visualization of the portal vein during splenic portography has been shown to coexist not only with patent portal veins, but also with forward direction in portal flow. Our own evidence denies reversal of flow in portal veins non-visualized during splenic portography but found to have forward flow when it was measured with the electromagnetic flowmeter.

Selective hepatic arteriography would be an ideally physiological means of demonstrating spontaneous reversal of portal flow. Indeed, it has been used successfully to demonstrate such spontaneous reversal in patients with Budd-Chiari syndrome, as well as reversal of flow in the hepatic limb of a side to side portacaval shunt. However, we have been unable to find a single report of spontaneous reversal in cirrhosis by the use of this technic.

In a large series of patients with cirrhosis submitted to hepatic intraparenchymal deposition of contrast medium, there is one false positive case of spontaneous reversal of portal flow which was negated by direct measurements of forward flow with the electromagnetic flowmeter. Another patient who was reported as showing a pattern compatible with spontaneous reversal of portal flow during intraparenchymal deposition of contrast medium was not submitted to the challenge of direct measurements with the electromagnetic flowmeter.

Actual measurements of magnitude and direction of portal flow in 273 patients with cirrhosis collected in the literature have shown no incidence of spontaneous reversal of portal blood flow. Results using electromagnetic flowmeters in patients under anesthesia have been confirmed by methods using computer analysis of high speed cineangiography in awake patients. There is, on the other hand, one isolated report of reversed direction, no magnitude indicated, of portal blood flow in cirrhosis. The authors of this article do not clarify the reasons for omitting the magnitude of this reversed flow in their report while including the magnitude of a forward portal flow in another patient.

Conclusions

In summarizing the data collected in this report, we cannot avoid the conclusion that the evidence for spontaneous reversal of portal flow in cirrhosis is weak and sparse. In our own personal judgement, the strongest support for this hypothesis derives from one patient whose direction of portal flow is said to have been found reversed during flowmeter determinations which did not include a report of the magnitude of the flow. What might be more important, there is no instance in which the presumed spontaneous reversal of portal flow has been confirmed by two independent methods of demonstration.

On the other hand, the evidence against spontaneous reversal of portal flow in cirrhosis seems to be overwhelming on both, qualitative and quantitative terms.

In the light of the findings discussed, and unless new and convincing evidence can be brought into the picture, we fail to see how we can serve the best interests of medicine in general and of our patients in particular by prolonging a debate concerning the clinical significance of an unproven phenomenon whose occurrence has been postulated, at best, on the basis of mere circumstantial evidence.

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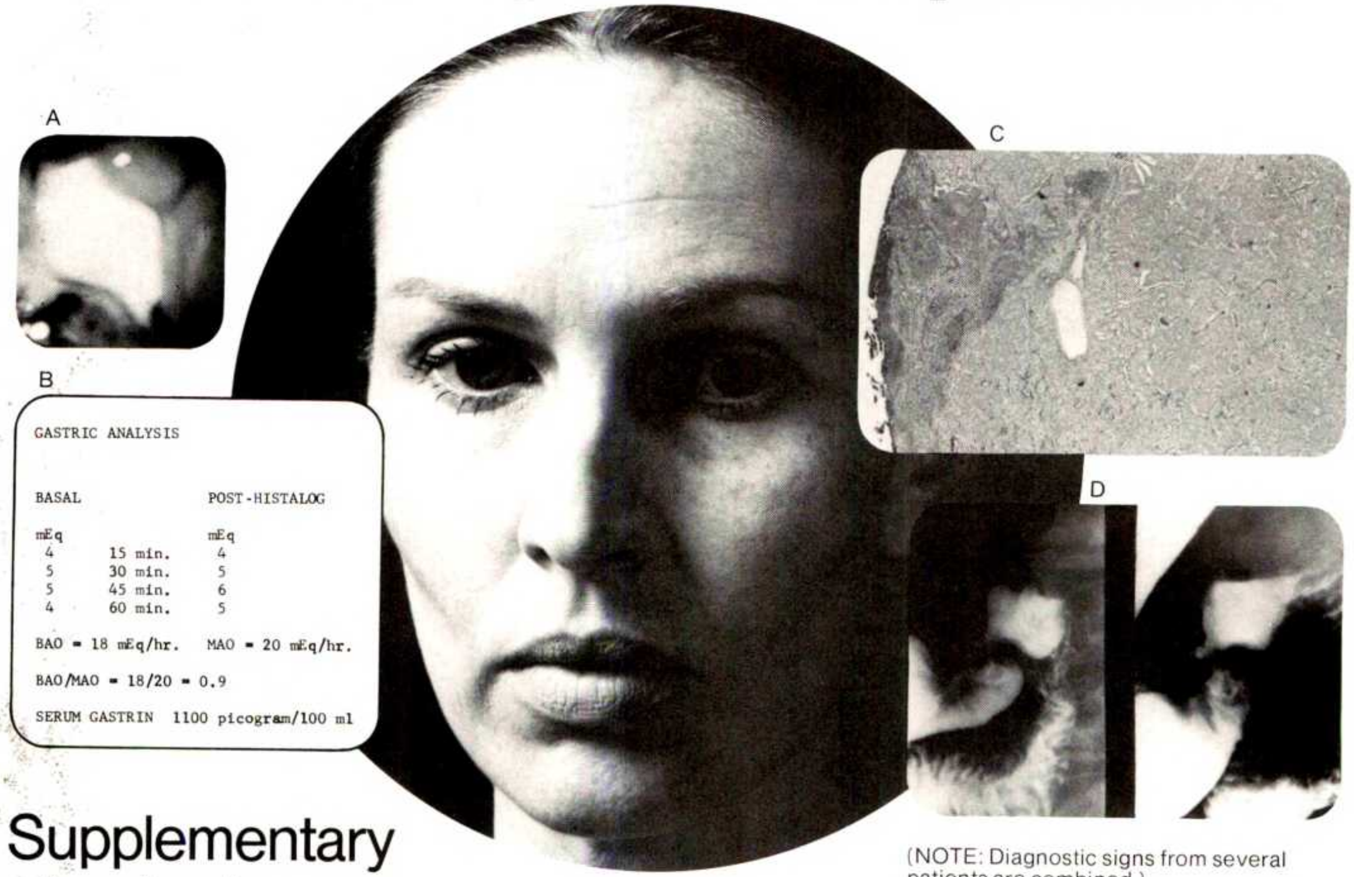

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GASTRIC ANALYSIS

BASAL                  POST-HISTALOG

mEq                    mEq
 4       15 min.        4
 5       30 min.        5
 5       45 min.        6
 4       60 min.        5

BAO = 18 mEq/hr.   MAO = 20 mEq/hr.

BAO/MAO = 18/20 = 0.9

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(NOTE: Diagnostic signs from several patients are combined.)

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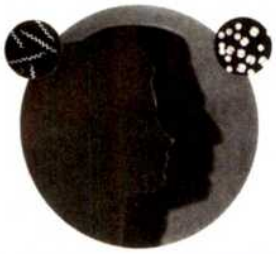

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THIS PROMOTIONAL CAMPAIGN HAS BEEN DISCONTINUED BY DIRECTION OF THE FOOD AND DRUG ADMINISTRATION.

MINOCIN® Minocycline Hydrochloride
Oral and Intravenous

DESCRIPTION: MINOCIN *minocycline hydrochloride* is a semi-synthetic derivative of tetracycline, 7-dimethylamino-6-deoxy-6-demethyltetracycline hydrochloride.

Intravenous: Each vial, dried by cryodesiccation, contains sterile Minocycline Hydrochloride equivalent to 100 mg. Minocycline. When reconstituted with 5 cc. of Sterile Water For Injection the pH ranges from 2.0 to 2.8.

ACTIONS: Microbiology. The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. Minocycline HCl is a tetracycline with antibacterial activity comparable to other tetracyclines with activity against a wide range of gram-negative and gram-positive organisms.

Tube dilution testing: Microorganisms may be considered susceptible (likely to respond to minocycline therapy) if the minimum inhibitory concentration (M.I.C.) is not more than 4.0 mcg./ml. Microorganisms may be considered intermediate (harboring partial resistance) if the M.I.C. is 4.0 to 12.5 mcg./ml. and resistant (not likely to respond to minocycline therapy) if the M.I.C. is greater than 12. 5 mcg./ml.

Susceptibility plate testing: If the Kirby-Bauer method of susceptibility testing (using a 30 mcg. tetracycline disc) gives a zone of 18 mm. or greater, the bacterial strain is considered to be susceptible to any tetracycline. Minocycline shows moderate *in vitro* activity against certain strains of staphylococci which have been found resistant to other tetracyclines. For such strains minocycline susceptibility powder may be used for additional susceptibility testing.

INDICATIONS: MINOCIN *minocycline HCl* is indicated in infections caused by the following microorganisms:

Rickettsiae: (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, tick fevers.)

Mycoplasma pneumoniae (PPLO, Eaton agent). Agents of psittacosis and ornithosis. Agents of lymphogranuloma venereum and granuloma inguinale. The spirochetal agent of relapsing fever (*Borrelia recurrentis*). The following gram-negative microorganisms:

Haemophilus ducreyi (chancroid), *Pasteurella pestis* and *Pasteurella tularensis*, *Bartonella bacilliformis*, *Bacteroides* species, *Vibrio comma* and *Vibrio fetus*, *Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended.

MINOCIN *minocycline HCl* is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Escherichia coli, *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*), *Shigella* species, *Mima* species and *Herellea* species, *Haemophilus influenzae* (respiratory infections), *Klebsiella* species (respiratory and urinary infections).

MINOCIN is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

Streptococcus species: Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

Diplococcus pneumoniae.

Staphylococcus aureus, skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infection.

When penicillin is contraindicated, tetracyclines are alternative drugs in the treatment of infections due to:

Neisseria gonorrhoeae, and *Neisseria meningitidis* (I.V. only), *Treponema pallidum* and *Treponema pertenue* (syphilis and yaws), *Listeria monocytogenes*, *Clostridium* species, *Bacillus anthracis*, *Fusobacterium fusiforme* (Vincent's infection), *Actinomyces* species.

In acute intestinal amebiasis, the tetracyclines may be a useful adjunct to amebicides.

MINOCIN is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral tetracyclines or with a combination of oral and topical agents.

Oral only: In severe acne, the tetracyclines may be useful adjunctive therapy. Minocycline is indicated in the treatment of asymptomatic carriers of *N. meningitidis* to eliminate meningococci from the nasopharynx.

In order to preserve the usefulness of MINOCIN *minocycline HCl* in the treatment of asymptomatic meningococcal carriers, diagnostic laboratory procedures, including serotyping and susceptibility testing, should be performed to establish the carrier state and the correct treatment. It is recommended that the drug be reserved for situations in which the risk of meningococcal meningitis is high.

Minocycline by oral administration is not indicated for the treatment of meningococcal infection.

CONTRAINDICATIONS: This drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

WARNINGS: In the presence of renal dysfunction, particularly in pregnancy, intravenous tetracycline therapy in daily doses exceeding 2 grams has been associated with deaths through liver failure.

When the need for intensive treatment outweighs its potential dangers (mostly during pregnancy or in individuals with known or suspected renal or liver impairment), it is advisable to perform renal and liver function tests before and during therapy. Also tetracycline serum concentrations should be followed.

If renal impairment exists, even usual oral or parenteral doses may lead to excessive systemic accumulation of the drug and possible liver toxicity. Under such conditions, lower than usual total doses are indicated, and if therapy is prolonged, serum level determinations of the drug may be advisable. This hazard is of particular importance in the parenteral administration of tetracyclines to pregnant or postpartum patients with pyelonephritis. When used under these circumstances, the blood level should not exceed 15 micrograms/ml. and liver function tests should be made at frequent intervals. Other potentially hepatotoxic drugs should not be prescribed concomitantly.

The use of tetracyclines during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracyclines, therefore, should not be used in this age group unless other drugs are not likely to be effective or are contraindicated.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema. Studies to date indicate that photosensitivity does not occur with MINOCIN *minocycline HCl*.

The antianabolic action of the tetracyclines may cause an increase in BUN. While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

CNS side effects including lightheadedness, dizziness or vertigo have been reported. Patients who experience these symptoms should be cautioned about driving vehicles or using hazardous machinery while on minocycline therapy. These symptoms may disappear during therapy and always disappear rapidly when the drug is discontinued.

Usage in Pregnancy. (See above "Warnings" about use during tooth development.)

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Usage in newborns, infants, and children. (See above "Warnings" about use during tooth development.)

All tetracyclines form a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg./kg. every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

PRECAUTIONS: As with other antibiotic preparations, use of this drug may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy should be instituted.

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

In long-term therapy periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed.

All infections due to Group A beta-hemolytic streptococci should be treated for at least 10 days.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

ADVERSE REACTIONS: Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region.

These reactions have been caused by both the oral and parenteral administration of tetracyclines. **Skin:** Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See "Warnings.") **Renal toxicity:** Rise in BUN has been reported and is apparently dose related. (See "Warnings.") **Hypersensitivity reactions:** Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythematosus. Bulging fontanels have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the drug was discontinued. **Blood:** Hemolytic anemia, thrombocytopenia, neutropenia and eosinophilia have been reported. **CNS:** (See "Warnings.") When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

DOSAGE AND ADMINISTRATION: ORAL. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided.

Concomitant therapy: Antacids containing aluminum, calcium, or magnesium impair absorption and should not be given to patients taking oral tetracycline.

Studies to date have indicated that the absorption of MINOCIN is not notably influenced by foods and dairy products.

In patients with renal impairment: (See "Warnings.") Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

In the treatment of streptococcal infections, a therapeutic dose of tetracycline should be administered for at least 10 days.

Adults: The usual dosage of MINOCIN *minocycline HCl* is 200 mg. initially followed by 100 mg. every 12 hours. Alternatively, if more frequent doses are preferred, two or four 50 mg. capsules may be given initially followed by one 50 mg. capsule four times daily.

Children: The usual dosage of MINOCIN *minocycline HCl* is 4 mg./kg. initially followed by 2 mg./kg. every 12 hours.

For treatment of syphilis, the usual dosage of MINOCIN should be administered over a period of 10-15 days. Close follow-up, including laboratory tests, is recommended.

Gonorrhea patients sensitive to penicillin may be treated with MINOCIN, administered as 200 mg. initially followed by 100 mg. every twelve hours for a minimum of 4 days, with post-therapy cultures within 2-3 days.

In the treatment of meningococcal carrier state recommended dose is 100 mg. every 12 hours for five days.

DOSAGE AND ADMINISTRATION: INTRAVENOUS. Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not adequate or tolerated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

Adults: Usual adult dose: 200 mg. followed by 100 mg. every 12 hours and should not exceed 400 mg. in 24 hours. The drug should be initially dissolved and then further diluted to 500–1,000 cc. with either Sodium Chloride Injection USP, Dextrose Injection USP, Dextrose and Sodium Chloride Injection USP, Ringer's Injection USP, or Lactated Ringer's Injection USP but not in other solutions containing calcium (a precipitate may form).

The reconstituted solutions are stable at room temperature for 24 hours without significant loss of potency. Any unused portions must be discarded after that period. The final dilution for administration should be administered immediately.

Children: Usual pediatric dose: 4 mg./kg. followed by 2 mg./kg. every 12 hours.

In patients with renal impairment: (See "Warnings.")

Total dosage should be decreased by reduction of recommended individual doses and/or by extending time intervals between doses.

HOW SUPPLIED: CAPSULES—Minocycline Hydrochloride equivalent to 100 mg. Minocycline. Hardshell purple and orange. Bottles of 50, 100 and Unit Dose 10 x 10's. Product No. 5301.

Minocycline Hydrochloride equivalent to 50 mg. Minocycline. Hardshell orange. Bottles of 100 and Unit Dose 10 x 10's. Product No. 5300.

SYRUP—Minocycline Hydrochloride equivalent to 50 mg. Minocycline per teaspoonful (5 cc.). Preserved with propylparaben 0.10% and butylparaben 0.06% with Alcohol USP 5% v/v. Custard-flavored in bottles of 2 fl. oz. Product No. 5313.

INTRAVENOUS—100 mg. vials of sterile cryodesiccated powder. Product No. 5305. (Combined 10/74)

MILITARY NSN 6505-00-149-0574 100 mg. I.V.

MILITARY NSN 6505-00-003-5112
(50's)
VA NSN 6505-00-003-5112A
100 mg. capsules

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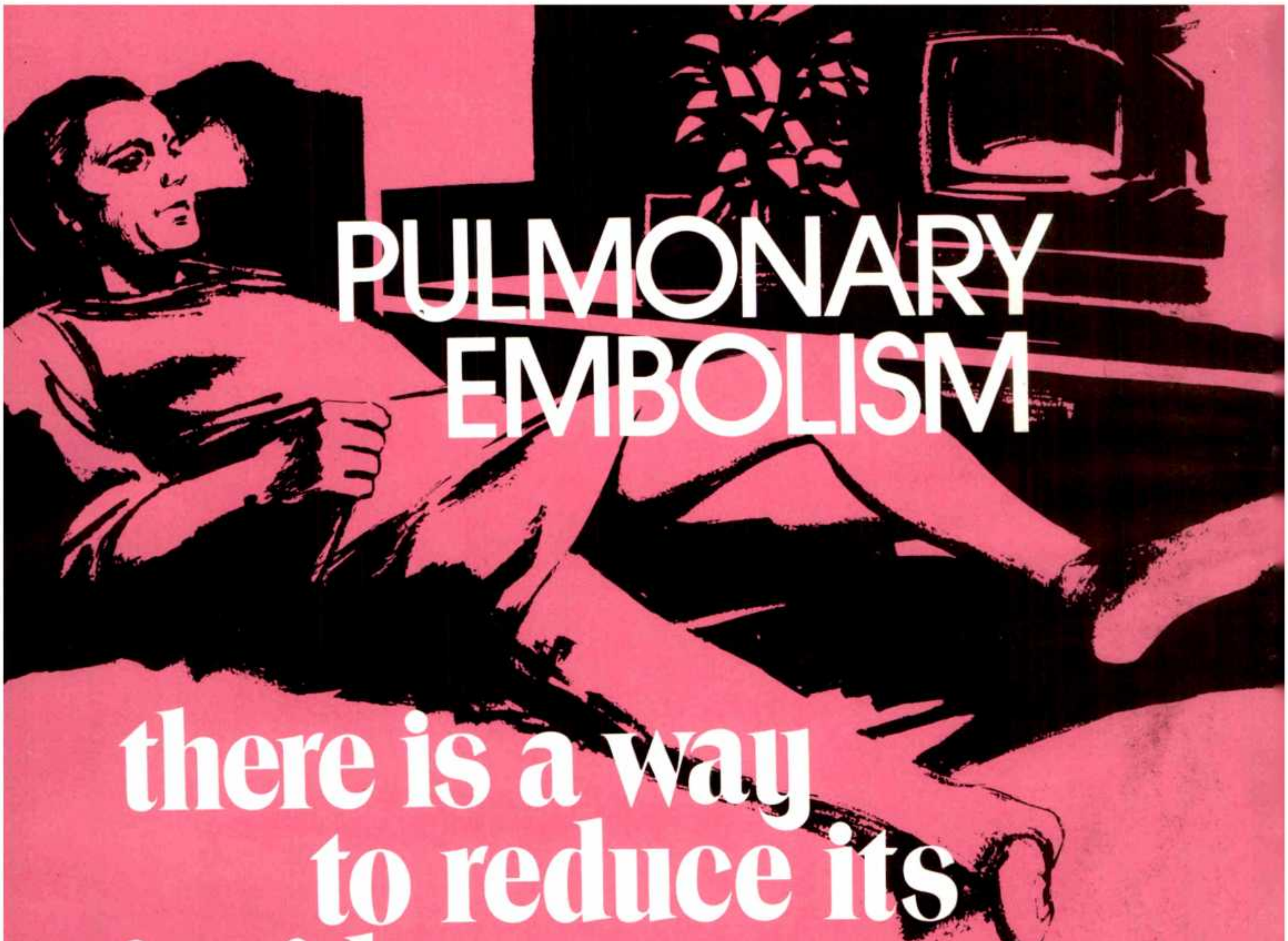

PULMONARY EMBOLISM

there is a way to reduce its incidence.

Pulmonary embolism is considered one of the most common causes of postoperative mortality, a frequent occurrence in the medical patient and the greatest single cause of maternal deaths due to childbirth.[1] Mortality figures of 50,000 to 150,000 are cited. 95% of pulmonary emboli originate as thrombi in the leg veins and pelvis.[2]

What causes the initial thrombus is open to debate. We know that venous stasis, changes in blood coaguability and vessel damage all may play a part, but which one—and how much?

Pulmonary embolism can be reduced through a rigidly implemented prophylactic program. The five basic elements are bed elevation, passive and active exercise, elastic compression, ambulation and anti-coagulants. All of these, or only those indicated for your patient, will lessen the danger of clot formation in the venous system.

Compression, by properly fitted elastic stockings, is a critical element in the program. When applied, compression acts on the deep veins of the legs where 90% of thrombi form. In 1973, Sigel et al documented that the velocity of blood in the femoral vein is increased when compression is applied.[3] It has been demonstrated that the blood velocity increase is maintained.[4] The conclusion made from the studies is that stasis, a commonly accepted contributing factor, is substantially reduced. Compression does work.

T.E.D.®
anti-embolism
stockings

T.E.D.®

anti-embolism stockings

The most effective application of compression is achieved with T.E.D. Anti-Embolism Stockings. T.E.D.'s are fabricated with proper functioning pressures knit into the stocking in the five critical areas of the leg: ankle, calf, popliteal space, lower thigh and upper thigh.

The stockings assure optimal compression while safeguarding the patient. In addition, Kendall backs their quality anti-embolism stockings with a program of continuing in-service, and knowledgeable Kendall representatives who can answer questions regarding stocking function, fit and application.

You can protect your patient from the possibility of pulmonary embolism with the added measure of T.E.D. Anti-Embolism Stockings.

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Antitumor Immune Response Following Injection of Neuraminidase-treated Sarcoma Cells

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Mice inoculated with MCA-10 sarcoma cells which had previously been incubated with Vibrio cholerae neuraminidase (VCN) demonstrated a significantly lower tumor incidence (9/26) than mice injected with untreated sarcoma cells (10/10) or sarcoma cells incubated with heat-inactivated neuraminidase (28/29) $p < .05$. Rechallenge of nontumor-bearing mice from the VCN group with untreated sarcoma cells resulted in a low tumor incidence (4/11), indicating that these mice had developed systemic immunity following the initial injection of VCN-treated tumor cells. These mice also demonstrated significant lymphocytotoxicity against MCA-10 target cells compared with normal control mice ($p < .05$). Subsequent cytotoxicity experiments, utilizing groin lymph node and splenic lymphocytes from mice five days following leg injection of VCN-treated, heat-inactivated VCN-treated or untreated MCA-10 cells, demonstrated that the mice injected with VCN-treated tumor cells demonstrated greater antitumor immunity both locally and systemically. This magnification of tumor immunity is postulated as the mechanism by which neuraminidase treated MCA-10 sarcoma cells grew less well in C57 mice than cells incubated with heat-inactivated VCN or cells left untreated.

TREATMENT OF MALIGNANT CELLS with Vibrio cholerae neuraminidase (VCN) has been shown to heighten their immunogenicity. It has been demonstrated experimentally that known nonimmunogenic leukemia L1210 cells, when treated with VCN, are rejected following inoculation into mice.[8] Furthermore, mice treated in this fashion are immune to subsequent challenge with untreated L1210 cells, which ordinarily grow in 100% of control mice.[1] Simmons et al.[11] have shown, in mice, that intratumor injection of VCN results in tumor regression. These investigators have also indicated that injection of VCN-treated malignant cells into sarcoma-bearing mice results in immunospecific tumor regression.[10]

Although the in vivo work reported overwhelmingly suggests that neuraminidase treatment increases the immunogenicity of malignant cells, it is unclear how this heightened immunogenicity is related to tumor rejection by a host which has not been previously exposed to that tumor. Whether the host immune response is more rapid following injection of VCN-treated tumor cells, or whether there is a quantitatively greater immune response is not known.

The purpose of these experiments is first, to demonstrate increased immunogenicity of a murine methylcholanthrene-induced fibrosarcoma following neuraminidase treatment and secondly, to determine, using lymphocytotoxicity assays, the effect of this increased immunogenicity on the host immune response.

Materials and Methods

An inbred strain of C_{57}B1/6N female mice, obtained from the Laboratory Aids Branch, National Institutes of Health, was utilized in all experiments. The tumor employed was a sarcoma (MCA-10) induced by an injection of methylcholanthrene in a female C_{57}B1/6N mouse and maintained by serial trocar transplantation.

Tumor cell suspensions were prepared by mincing tumor in 0.25% trypsin and agitating for 20 minutes. This was repeated twice, and the supernatant from the second trypsinization was centrifuged at 1,500 rpm at 4C for ten minutes. The cells were resuspended and counted in a hemocytometer. Viability was tested by ability to exclude 0.05% trypan blue, and cell suspensions of 80–90% viability were obtained.

Lymphocyte-mediated cytotoxicity studies were accomplished by routine methods.[7,14] MCA-10 sarcoma cells

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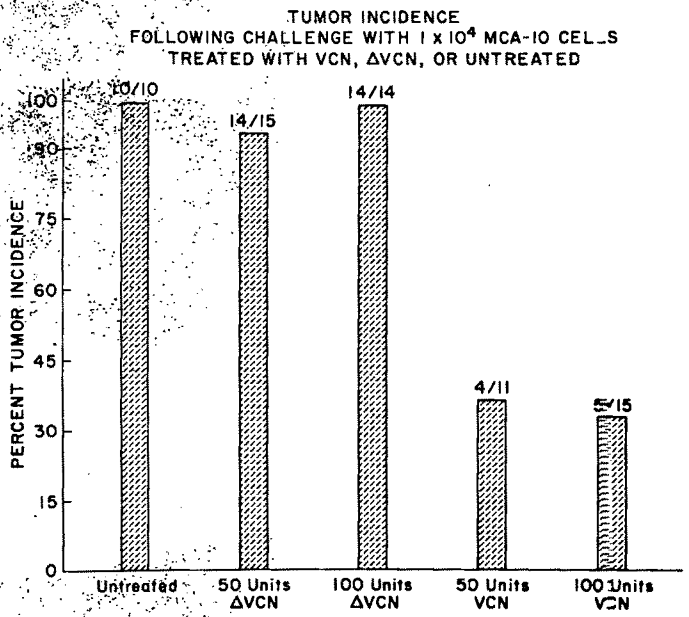

FIG. 1. Experiment 1. Tumor incidence following intramuscular challenge of C57 mice with VCN-treated, ΔVCN-treated or untreated MCA-10 sarcoma cells.

were plated out in No. 3034 Microtest tissue culture plates* (approximately 100 cells per well) and 24 hours later, lymphocytes were added to a ratio of 100:1 to target cells. The plates were incubated at 37C for 48 hours in a 5% CO_2 atmosphere, following which lymphocytes were removed, the plates were stained, and the remaining target cells were counted. Forty-two replicate wells were included for each test group. Cytotoxic indices were calculated for each replicate well by the following method:

$$CI = \frac{\text{No. of viable control cells—No. of viable test cells}}{\text{No. of visible control cells}}$$

A cytotoxic index of greater than 0.10 was significant ($p < .05$).

Vibrio cholerae neuraminidase† containing 500 units of enzyme/ml was diluted to a concentration of 50U/ml and 100U/ml with acetate buffer (0.05M sodium acetate, 0.154M NaCl, and 0.005M $CaCl_2$ at pH 5.6). Inactivation of VCN was achieved by heating to 56C for 30 minutes. Single cell suspensions of the MCA-10 sarcoma were washed and resuspended to a final concentration of 1x10⁶ cells/ml./50U VCN and 1x10⁶ cells/ml./100U VCN. Length of incubation at 37C was varied according to the experimental design.

Experimental design

Experiment 1. Adult C57 mice were divided into five groups as follows:

	Tumor incidence following rechallenge	Average number of viable target cells/well
VCN-TREATED	**4/11**	**79.7 ± 2.92**
UNTREATED	**15/15**	**107.6 ± 3.35**

FIG. 2. Experiment 1. Results of tumor rechallenge of nontumor-bearing mice from the VCN groups and cytotoxic activity of splenic lymphocytes of nontumor-bearing mice from the VCN groups.

1. Control—Ten mice receiving 1x10⁴ MCA-10 cells intramuscularly in the right leg.
2. ΔVCN—Fifteen mice receiving 1x10⁴MCA-10 cells incubated for 30 minutes with 50U heat-inactivated VCN (ΔVCN).
3. ΔVCN—Fourteen mice receiving 1x10⁴ MCA-10 cells incubated for 30 minutes with 100UΔVCN.
4. VCN—Eleven mice receiving 1x10⁴ MCA-cells incubated for 30 minutes with 50U VCN.
5. VCN—Fifteen mice receiving 1x10⁴ MCA-10 cells incubated for 30 minutes with 100U VCN.

Animals were observed twice weekly for tumor incidence for a period of one month. At this point, nontumor-bearing mice from the VCN groups were either challenged with 1x10⁴ untreated MCA-10 cells or were sacrificed, and their splenic lymphocytes were tested for cytotoxic capacity against MCA-10 tissue culture target cells. Control lymphocytes for the cytotoxicity test were obtained from the spleens of normal untreated mice.

Experiment 2. Mice were divided into three groups as follows:

1. VCN—Ten mice injected with 1x10⁴ MCA-10 sarcoma cells incubated with 50U VCN for 20 minutes.
2. ΔVCN—Ten mice injected with 1x10⁴ MCA-10 sarcoma cells incubated with 50UΔVCN for 20 minutes.
3. Control—Ten mice injected with 1x10⁴ untreated MCA-10 cells.

Five days following tumor injection, lymphocytes from groin lymph nodes of the tumor-injected leg and splenic lymphocytes were tested for cytotoxic activity against MCA-10 tissue culture target cells.

Experiment 3. The experimental design was identical to that of Experiment 2, except that MCA-10 cells were incubated with VCN and ΔVCN for 15 minutes.

Results

For experiment 1, Fig. 1 shows the results of tumor challenge. Tumor incidence for mice inoculated with untreated sarcoma cells (10/10) and cells incubated with either 50UΔVCN (14/15) or 100UΔVCN (14/14) was virtually 100%. However, mice receiving injections of MCA-10 cells treated with VCN showed significantly lower tumor

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*Falcon Plastics, Oxnard, California.

†General Biochemicals, Chagrin Falls, Ohio.

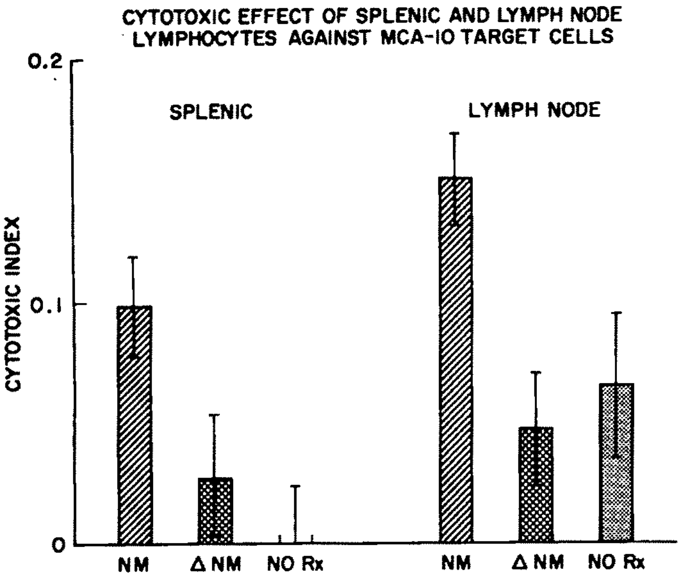

FIG. 3. Experiment 2. Lymphocytotoxicity of lymph node and splenic lymphocytes of mice from VCN-treated, ΔVCN-treated and untreated groups.

growth. These same neuraminidase-treated tumor cells were also capable of inducing tumor immunity in the host, as demonstrated by both in vivo (rejection of tumor rechallenge) and in vitro methods (demonstration of significant lymphocytotoxicity against MCA-10 target cells). The effects of neuraminidase were observed whether cells were incubated with 50U or 100U of VCN.

Experiments 2 and 3 were designed to determine the mechanism by which neuraminidase-treated tumor cells are more readily rejected than untreated cells. In addition, an attempt was made to determine if decreasing the time of tumor cell incubation with VCN affected tumor cell immunogenicity. The results of both experiments indicate that only lymphocytes from mice inoculated with VCN-treated tumor cells showed significant cytotoxicity against MCA-10 target cells. Lymphocytes from mice injected with untreated or ΔVCN-treated tumor cells were not significantly cytotoxic. The duration of incubation did not affect these results. The data suggest that neuraminidase-treated cancer cells are capable of evoking a greater immune response not only from the lymphocytes of the regional lymph nodes, but also they appear to be able to induce greater systemic immunity. Therefore, neuraminidase-treated sarcoma cells appear to be able to stimulate the host's immunity at a time when the number of tumor cells in the host is small. These are ideal circumstances for tumor rejection.

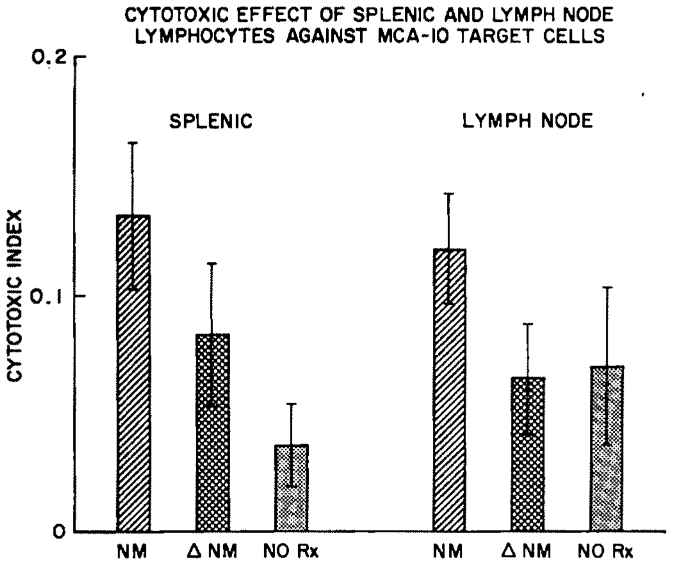

FIG. 4. Experiment 3. Lymphocytotoxicity of lymph node and splenic lymphocytes of mice from VCN-treated, ΔVCN-treated and untreated groups.

Other factors may be responsible for the low tumor incidence following injection of neuraminidase-treated tumor cells into the host. It has been shown that neuraminidase-treated normal[3] and malignant[14] cells are more susceptible to specific immune cytolysis by lymphocytes and sera than are untreated cells. Thus, not only are neuraminidase-treated malignant cells capable of immunizing the host (as suggested by the present experiments), but also they appear to be more susceptible to immune cytolysis.

Other mechanisms may be responsible for cytolysis of neuraminidase-treated tumor cells in vivo. Ray et al.[5] have demonstrated that the terminal components of activated complement (C3-C9) are capable of lysing VCN-treated rabbit lymphocytes in the absence of cytotoxic antibody. Untreated lymphocytes did not demonstrate this susceptibility. It is not unreasonable to assume that VCN-treated tumor cells might similarly show this susceptibility to activated complement. Removal of sialic acid from cell surfaces following neuraminidase treatment may increase in vivo cytolysis as a result of increased phagocytosis of these cells,[15] or facilitation of the physical target cell-lymphocyte interaction.[2]

Nevertheless, it appears that stimulation of tumor immunity by VCN-treated malignant cells is the most important effect of neuraminidase in the destruction of tumor cells in vivo. The detailed studies of Simmons et al.[6,9,12] have clearly shown that, in mice, neuraminidase-induced tumor regression is the result of stimulation of the host's immunity to tumor specific antigens. The present experiments support the above findings by indicating that mice injected with neuraminidase-treated sarcoma cells demonstrate a more potent local and systemic lymphocytotoxicity response to that sarcoma.

From these experiments it can be concluded that rejection of neuraminidase-treated sarcoma cells by mice which had not previously been exposed to the tumor is primarily the result of magnification of the antitumor immune response. Of lesser importance, may be increased susceptibility of neuraminidase-treated cells to cytolysis.

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Suppression of Leukocyte Chemotaxis in vitro by Chemotherapeutic Agents Used in the Management of Thermal Injuries

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Polymorphonuclear leukocytes from burned patients exhibit suppressed chemotaxis possibly related to the susceptibility of such patients to opportunistic infection. This study assesses the effect of normal serum upon burn-suppressed leukocytes and the effects of three commonly used topical chemotherapeutic agents upon the chemotaxis exhibited by granulocytes from normal controls. In vitro incubation with normal serum restored chemotaxis to normal in the suppressed granulocytes from burned patients. The serum factor responsible for this restoration was heat labile. Serum albumin alone did not exhibit this effect. Both mafenide and silver sulfadiazine suppressed the chemotactic function of granulocytes obtained from normal controls, while silver nitrate exhibited no such activity. Studies of the chemotactic function of control granulocytes after incubation with sera from burned patients yielded similar results; only the sera from patients treated with silver nitrate failed to suppress normal leukotaxis. The chemotactic impairment found in leukocytes from burned patients, however, while related to burn size and predictive of prognosis, did not vary with the agent used for the topical therapy. These data suggest the presence of a reversible intrinsic defect in leukotaxis consequent to burn injury, related to some factor deficient in burn serum. In addition, extrinsic impairment of normal granulocyte leukotaxis by two commonly used chemotherapeutic agents is demonstrated.

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THE USE of topical chemotherapeutic agents to control bacterial invasion in extensive burn wounds has become an accepted method of treatment. Mafenide acetate (Sulfamylon®), silver nitrate and silver sulfadiazine (Silvadene®) are widely used agents for such topical treatment. The advantages and disadvantages of each agent have been described and their effectiveness in decreasing the incidence of pseudomonas burn wound sepsis is well established. Despite this decreased incidence of pseudomonas burn wound sepsis, the mortality from extensive thermal injury remains high. The use of topical chemotherapy has been associated with increased frequency of infection by other opportunistic organisms. Infection remains the most frequent cause of death in patients who have sustained large burns.

The susceptibility of burn patients to opportunistic infection is not understood. Several defense mechanisms are known to be impaired, including the epithelial barrier, immune mechanisms and leukocyte function. We have introduced an assay of leukocyte chemotaxis to assess one aspect of polymorphonuclear leukocyte function in thermally injured patients and have demonstrated an inverse correlation between leukocyte chemotaxis and burn size.[8] In addition, suppression of leukocyte chemotaxis has been predictive of mortality in burn patients. This study of the mechanism of chemotactic suppression following burn injury assesses the effects of normal serum and of topical chemotherapeutic agents upon granulocyte chemotaxis.

Materials and Methods

Preparation of Leukocytes

On the day of testing 10 cc of heparinized blood (200 units heparin per 10 cc blood) was collected in a glass syringe. The aliquant was placed in an equal volume of clinical dextran (6%) in physiologic saline solution, containing glucose (400 mg/500 ml) and heparin (20 mg/100

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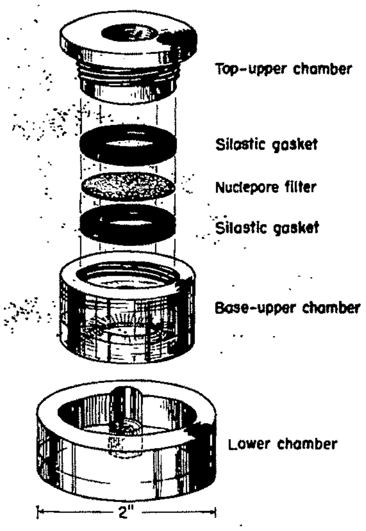

FIG. 1. Chemotactic chamber.

ml). Erythrocyte-mononuclear sedimentation was accomplished in a 50 ml conical tube at 37 C for 45 minutes. The leukocyte rich supernatant was removed with a Pasteur pipette and used within one hour of preparation. Average yields of 10^8 cells were obtained from 10 ml of blood. Ninety-nine per cent viability was confirmed by the trypan blue exclusion method after sedimentation.

Chemotactic Agent

Previous studies by Baum and Mouat[3] have demonstrated a mixture containing two parts of casein solution and one part of human serum to furnish reliable chemotactic attraction. Casein was prepared in a concentration of 5 mg/ml in Hank's solution. Human serum, type AB, from healthy donors was used throughout the study. The serum was obtained in the following manner: 1) 500 ml of peripheral blood was removed via the antecubital vein and placed in 50 ml conical tubes and allowed to clot at room temperature; 2) After clot retraction, the sample was centrifuged at 2000 *g* and the serum removed; 3) The serum was stored at −73 C in 3 ml aliquots.

Evaluation of Leukocyte Chemotaxis

Perspex chambers similar to Boyden's design were constructed (Fig. 1). Two ml of leukocyte-rich supernatant were diluted with 8 ml of Hank's solution and 2 ml of this mixture, containing approximately 4 × 10 cells, were placed in the upper chamber and 1.5 ml of chemotactic agent (casein-serum mixture) were placed in the lower chamber. A nuclepore* filter, 0.5 μ pore size, 25 mm diameter was interposed between the upper and lower chambers. The chamber was incubated at 37 C for 120 minutes. The nuclepore filter was removed, stained with Wright-Giemsa stain for 4 minutes, Wright's buffer for 4 minutes, cleared with xylene and mounted with xylene-permount (3:1) ratio on a glass slide. The nuclepore filter was examined microscopically under high power and the cells migrating through the nuclepore filter (bottom side) were counted as were the cells remaining on the starting side (top side) in each microscopic field. A total of 400 cells was counted. Chemotaxis was evaluated in the following manner, negating the necessity to count the cells before placement in the upper chamber.

$$\text{Chemotactic index} = \frac{\text{Number cells (attracting side)} \times 1000}{\text{number cells (starting side)}}$$

Leukocytes from thermally injured patients were compared with cells from normal healthy volunteers and the functional chemotactic index expressed as the per cent of the chemotactic index of the control leukocytes:

$$\text{Functional chemotactic index} = \frac{\text{chemotactic index burn patient}}{\text{chemotactic index normal volunteer}} \times 100$$

Duplicate chambers were used for each patient sample and simultaneous control samples were also performed in duplicate.

Preparation of Patient Serum

On the morning of each test, 10 cc of peripheral blood was obtained and allowed to clot. After clot retraction the sample was centrifuged at 2000 *g* and the serum removed. The serum was stored at −73 C or used within one hour of preparation.

Experimental Group

Studies were performed on 46 thermally injured patients with a mean burn size of 50.9% of total body surface (range 14.5–92.0%). The overall mortality among these patients was 65.2%. The mean burn size in those patients who expired was 59.0% (range 31.5–92.0%) while the surviving patients had an average burn size of 35.9% (range 14.5–70.5%). Autopsy examination was performed on 25 of the 30 nonsurviving patients. The mean day of death was 14.9 days (range 3–38 days). Among the autopsied cases, infection as the major cause of death occurred in 23 of the 25 cases (92.0%). Septic complications included pneumonia, burn wound sepsis, and septicemica. The mean day of clinical diagnosis of the septic complications was 9.8 days (range 3 to 19 days). None of the 16 surviving patients had systemic sepsis.

The patients' cells were tested at admission and then weekly until discharge or expiration. The patients were treated with topical mafenide acetate 10% ointment (Sulfamylon®), silver nitrate 5% solution in dressings, or silver sulfadiazine 1% cream (Silvadene®) using standard procedures of the Institute of Surgical Research.

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*Nuclepore Corporation, 7035 Commerce Circle, Pleasanton, California 94566.

Evaluation of Effect of Burn Serum on Leukocyte Chemotaxis

The leukocyte rich supernatant obtained from normal volunteers was incubated in 1:1 ratio for 20 minutes at 37 C with serum obtained from thermally injured patients, normal serum obtained from healthy type AB donors or Hank's solution. This suspension was then diluted with Hank's solution and 2 ml of this mixture, containing approximately 4 × 10^6 cells were placed in the upper compartment of the chamber for evaluation of leukocyte chemotaxis.

Evaluation of Effect of Topical Chemotherapeutic Agents on Leukocyte Chemotaxis

The topical agents were dissolved in Hank's solution and incubated with 2 ml of leukocyte rich supernatant obtained from normal volunteers with final concentrations of: mafenide acetate 10 mg%, and 100 mg%, p. carboxybenzenesulfonamide 10 mg%, sulfadiazine 5 mg%, sodium sulfadiazine 5 mg%. In addition acetazolamide (Diamox®), 50 μg/ml and 100 μg/ml and gentamycin (Garamycin®) 4 μg/ml were also included in duplicate chemotactic chambers. Hank's solution without added drug was used in the same manner for control studies, which were performed in duplicate.

Evaluation of Effect of Dialyzed Burn Serum on Leukocyte Chemotaxis

Serum from thermally injured patients was dialyzed in cellulose casing (Visking, medical grade 23/32)* with diphosphate buffer 0.15 M, ph 7.4 for 48 hours at 4 C. The dialyzed serum was then added to 2 ml of the leukocyte rich supernatant from normal volunteers in 1:1 ratio and the mixture incubated at 37 C for 20 minutes. After dilution with Hank's solution, 2 ml of the mixture, containing 4 × 10^6 cells, was placed in the upper compartment of the chemotactic chamber for evaluation of leukocyte chemotaxis. Normal AB serum was maintained at 4 C for 48 hours and then incubated in the same manner as a simultaneous control.

Evaluation of Effect of Normal Serum on Chemotaxis

Serum from normal AB donors was used to assess the effect of normal serum upon leukocytes from burned patients. AB serum was added to 2 ml of the leukocyte rich supernatant in 1:1 ratio and the mixture incubated at 37 C for 20 minutes. After dilution with Hank's solution, 2 ml of the mixture, containing approximately 4 × 10^6 cells, was placed in the upper compartment of the chemotactic chamber for evaluation of leukocyte

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*Visking Company, Chicago, Illinois.

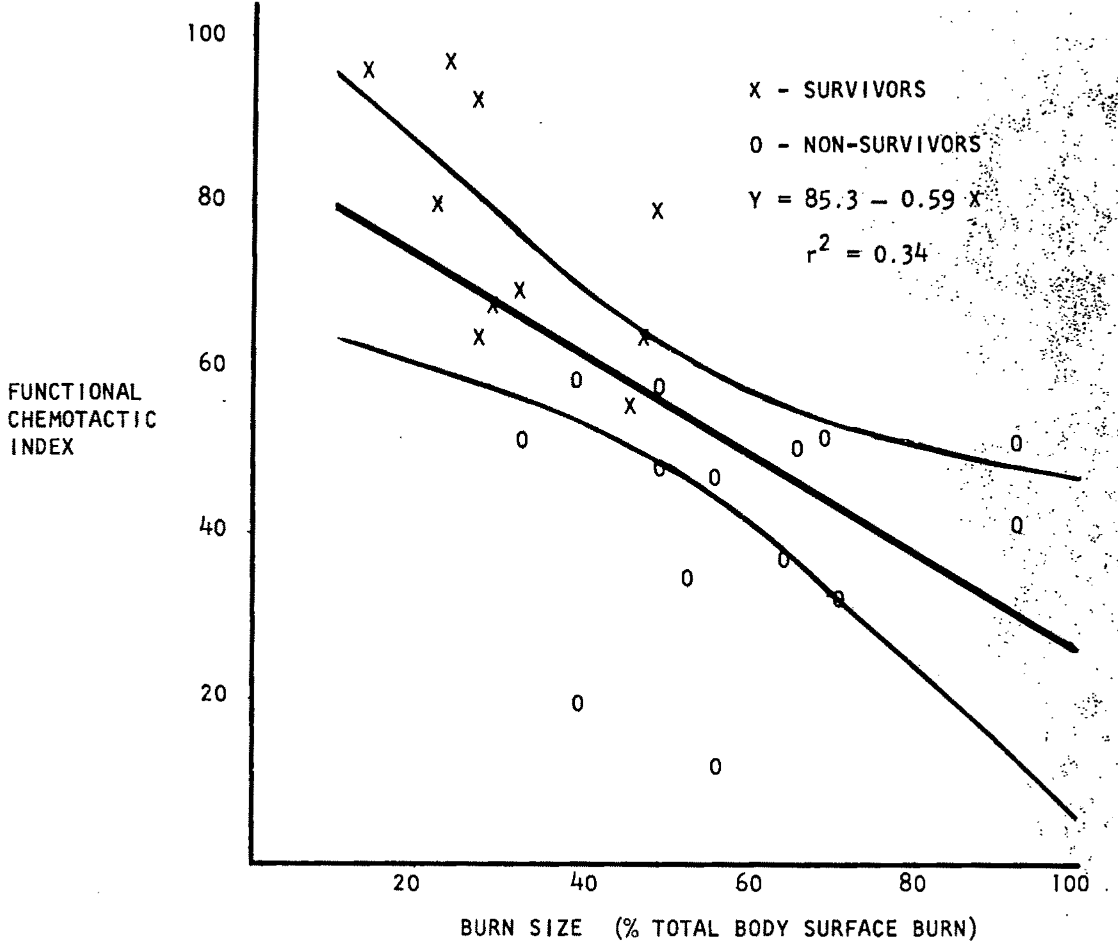

FIG. 2. Functional chemotactic index versus burn size during first 72 hours postburn.

TABLE 1. *Functional Chemotactic Index after 72 hours*

	Survivors	Non-Survivors
Patients	12	23
Determinations	36	3[illegible]
Functional Chemotactic Index	97.7%	39.[illegible]%
Significance	P = < 0.01	
Range	61.2-130	14.[illegible]-75
Burn Size Mean	44.6%	57.[illegible]%
Range	25.5-70.5	31.[illegible]-92

chemotaxis. Simultaneous controls were run using Hank's solution instead of serum.

Evaluation of Effect of Heated Normal Serum on Leukocyte Chemotaxis

Serum from normal AB donors was heated at 56 C in a water bath for 20 minutes. The leukocyte rich supernatant from thermally injured patients was incubated with the heated AB serum at 37 C for 20 minutes. This suspension was diluted with Hank's solution and 2 ml of this mixture containing approximately 4 × 10^6 cells were placed in the upper compartment of the chemotactic chamber for evaluation of leukocyte chemotaxis. As controls, Hank's solution and normal serum type AB were incubated in duplicate.

Evaluation of the Effect of Albumin on Leukocyte Chemotaxis of Thermally Injured Patients

Two ml of the leukocyte rich suspension obtained from thermally injured patients was incubated at 1:1 ratio with salt poor, human albumin* (25 g/100 cc) for 20 minutes. The suspension was diluted with 5 ml Hank's solution and 2 ml of this mixture (approximately 4 × 10^6 cells) was placed in the upper chamber of the chemotactic chamber for evaluation of leukocyte chemotaxis. As controls, incubation with Hank's solution and normal serum type AB was performed in duplicate.

TABLE 2. *Effect of Burn Serum on Normal Leukocyte Chemotaxis*

	Sulfamylon	Silver Nitrate	Silver Sulfadiazine
Number	27	3	14
Mean Functional Chemotactic Index	54.0%*	111.8%	42.4%*
Standard Error	±3.8	±5.8	±2.3
Burn Size Mean	46.3%	40.8%	65.0%
Range	18-70.5	35.5-48	30.5-96

*Significantly different from control, P < 0.01.

Results

Chemotaxis in Thermally Injured Patients

As simultaneous daily control values, the chemotactic index was measured in a total of 44 normal healthy volunteers (ages 23–54 years). A mean value of 764.4 with 95% confidence limits of 750–780 was observed.

During the first 72 hours following injury, 24 patients were studied. Burn size and functional chemotactic index were inversely related, with a regression of y = 85.3 −

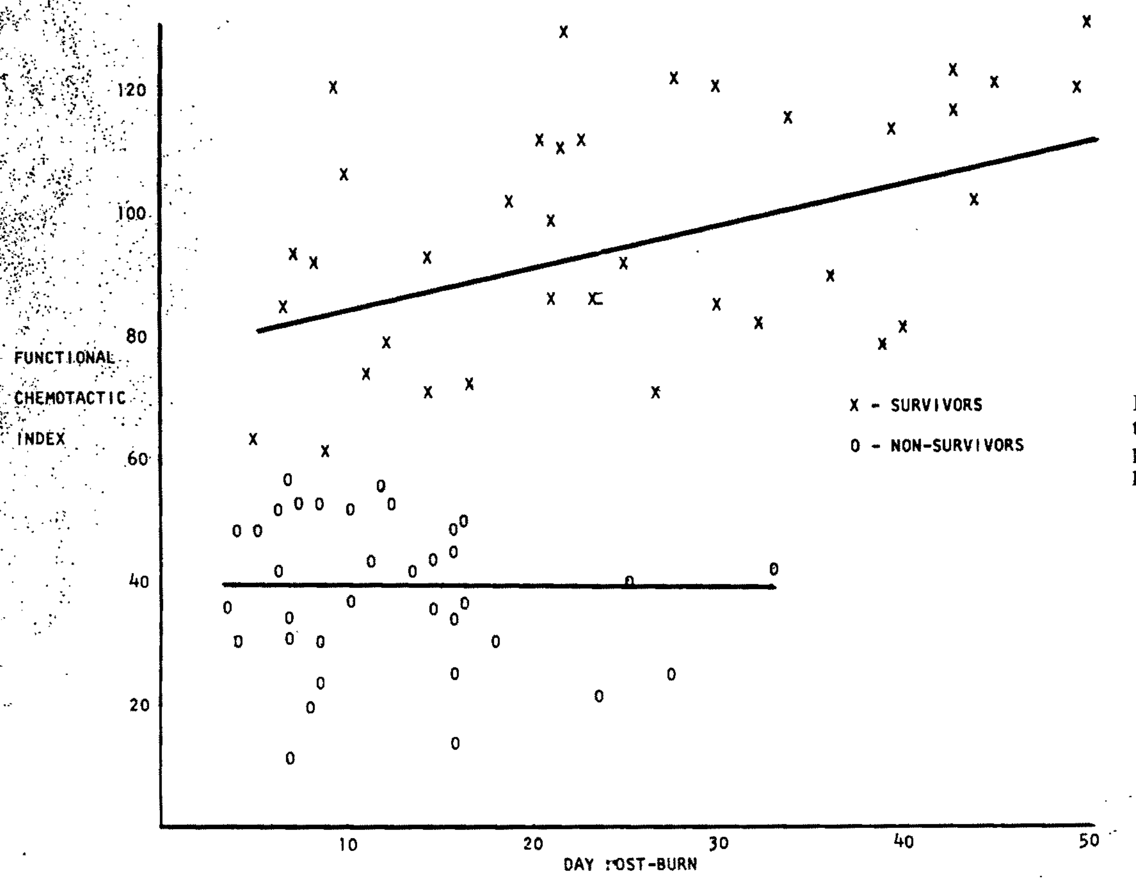

FIG. 3. Functional chemotactic index versus day postburn after 72 hours postburn.

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*Cutter Laboratories, Berkeley, California.

TABLE 3. *Effect of Chemotherapeutic Agents in vitro on Normal Leukocyte Chemotaxis*

Chemotherapeutic Agent	Concentration	No.	Mean Functional Chemotactic Index
Mafenide Acetate	10 mg%	6	68.5% ± 1.9
Mafenide Acetate	100 mg%	6	54.7% ± 2.7
P-Carboxybenzene-sulfonamide	10 mg%	6	58.1% ± 2.0
Sodium Sulfadiazine	5 mg%	4	36.7% ± 2.0
Sulfadiazine	5 mg%	4	24.6% ± 3.6
Gentamycin	4 μg/ml	4	97.8% ± 7.4

TABLE 4. *Effect of Dialyzed Burn Serum on Normal Leukocyte Chemotaxis*

	Sulfamylon		Silver Sulfadiazine	
	Burn Serum	Dialyzed Burn Serum	Burn Serum	Dialyzed Burn Serum
Number	10	10	9	9
Mean Functional Chemotactic Index	43.7%	84.0%	42.0%	82.8%
Significance	P = < 0.001		P = < 0.01	
Burn Size Mean	50.2%		69.7%	
Range	18.0-70.5		30.5-96.0	

0.59 x (y= functional chemotactic index, x = burn size), and $r^2 = 0.34$ (Fig. 2).

After 72 hours, the patients separated into two groups, survivors and nonsurvivors, with surviving patients demonstrating improvement in leukocyte chemotactic function during their hospital courses (Fig. 3). The nonsurviving patients demonstrated neither significant increase or decrease in leukocyte chemotaxis from admission until death. The average functional chemotactic index in the surviving groups was 97.7, SE ± 2.3; whereas the average in the nonsurviving was 39.9, SE ± 2.3 (Table 1). No patient with a functional chemotactic index below 60 beyond 72 hours after injury survived; only one patient with an index greater than 60 expired. Statistical comparison revealed a significant difference between the mean indices of these groups (P<<0.01).

Diminished chemotactic function was observed prior to clinical infection in all patients who ultimately succumbed to infection. The onset of clinical infection was not associated with any change in the functional index. Functional chemotactic index did not vary with either the agent used for topical chemotherapy or with other identifiable differences in treatment. Age and sex were also without effect.

Effect of Burn Serum on Normal Leukocyte Chemotaxis

Serum obtained from 27 burn patients treated with mafenide acetate with a mean burn size of 46.3% total body surface (range 18.0–75%) produced significant suppression (P<<0.01) of chemotaxis of normal control leukocytes, decreasing the chemotactic index to 54.0% of control values (Table 2). The serum of 14 burn patients treated with silver sulfadiazine (mean total body surface burn 65.0%, range 30.5–96.0%) also suppressed normal control leukocyte chemotaxis to 42.4% of control (P <<0.01). However, the silver nitrate treated patients' serum produced no suppression of normal leukocyte chemotaxis although burn size was similar to the mafenide acetate treated group. Simultaneous control AB serum had no effect on normal leukocyte chemotaxis.

Effect of Topical Chemotherapeutic Agents on Normal Leukocyte Chemotaxis

Mafenide acetate and its metabolite, p-carboxybenzenesulfonamide at a physiologic concentration (10 mg %) usually obtained during treatment of major thermal injuries produced significant suppression (P <0.01) of normal control leukocyte chemotaxis to 68.5% (SE ±1.9) and 58.1% (SE ± 2.0) respectively, of baseline values (Table 3). Increasing the concentration of mafenide acetate to 100 mg% resulted in a more pronounced depression (54.7% SE ± 2.7) of normal leukocyte chemotaxis (P <0.01). Sulfadiazine and sodium sulfadiazine at concenration of 5 mg % produced marked suppression of normal leukocyte chemotaxis to 24.6% and 32.8% respectively. Gentamycin at a concentration of 4 μg/ml produced no significant change of normal leukocyte chemotaxis. The suppressions exhibited by adding the topical agent directly to the cell suspension are similar to the suppressions obtained by incubating with burn serum from thermally injured patients treated with these agents.

Effect of Acetazolamide on Normal Leukocyte Chemotaxis

Since mafenide acetate (Sulfamylon®) inhibits carbonic anhydrase, the effect of acetazolamide (Diamox®) on normal leukocyte chemotaxis was also evaluated at concentrations of 50 μg/ml and 100μg/ml. Animal carbonic anhydrase inhibition occurs at serum levels of 50 μg/ml.

TABLE 5. *Effect of Normal Type AB Serum on Leukocyte Chemotaxis of Thermally Injured Patients*

	Baseline	Normal Serum Incubation
Number	33	33
Mean Functional Chemotactic Index	61.1%	107.7%
Standard Error	±5.7	±4.8
Significance	P = < 0.01	
Burn Size	46.8% (Range—14.5-70.5)	

TABLE 6. *Effect of Heated AB Serum on Leukocyte Chemotaxis*

	Baseline	Normal Serum Incubation	Heated Serum Incubation
Number	6	6	6
Mean Functional Chemotactic Index	70.6%	102.6%	72.5%
Standard Error	±8.8	±3.3	±10.7
Significance*	——	P = < 0.05	N.S.
Burn Size	50% (Range 32-63%)		

*Multiple comparisons with Baseline (Scheffe Test).

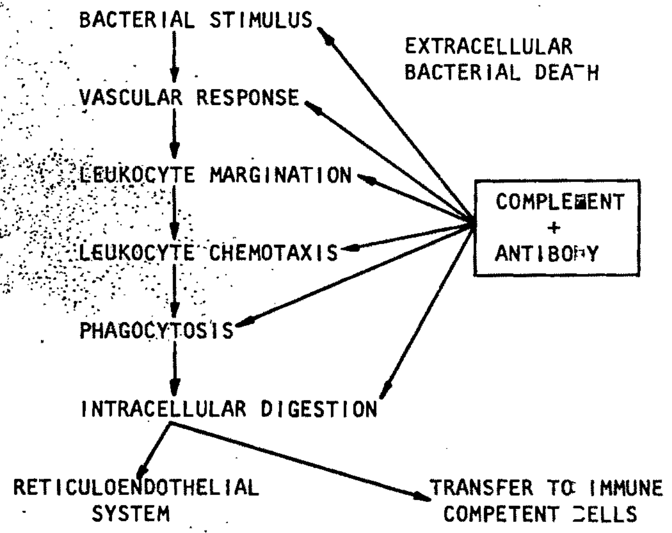

FIG. 4. Host defense mechanism against bacterial invasion.

Acetazolamide at 50μg/ml produced no suppression of normal leukocyte chemotaxis; whereas at 100μg/ml there was slight depression, to 85.2% of control ($P < 0.01$). We conclude that carbonic anhydrase inhibition by mafenide acetate was not responsible for the depression seen with burn serum or mafenide acetate.

Effect of Dialyzed Burn Serum on Normal Leukocyte Chemotaxis

Non-dialyzed burn serum obtained from 10 patients treated with mafenide acetate with a mean burn size of 50.2% total surface (range 18.0–70.5%) produced suppression of normal leukocyte chemotaxis to 13.9% of control values. Dialyzing the burn serum for 48 hours with a phosphate buffer significantly reduced ($p \leqslant 0.01$) the degree of suppression by burn serum to a mean value of 84.0% (Table 4). Dialyzed burn serum obtained from nine patients treated with silver sulfadiazine (mean burn size 69.7%, range 30.5–96%) also produced significantly ($P \leqslant 0.01$) less suppression than did the non-dialyzed burn serum with mean values increasing from 42.0% to 82.8%. These studies suggest that dialysis removed a chemotaxis-suppressing substance or substances, presumably the topical therapeutic agents mafenide acetate and silver sulfadiazine.

Effect of Normal Serum on Burn Leukocyte Chemotaxis

In 33 patients with a mean burn size of 46.8% total body surface area (range 14.5–70.5%) and having a mean baseline chemotactic index of 61.1% (SE ± 5.7) there was a marked increase of leukocyte chemotaxis after incubation with normal AB serum (Table 5). Levels increased to 107.7% (SE ± 4.8) of simultaneous normal controls Normal AB serum incubated with normal cells had no effect on leukocyte chemotaxis. The improvement of chemotaxis by normal serum was not related to the agent being used for topical chemotherapy and was not a dilution effect, since similar dilution with Hank's solution in the control runs had no effect.

Effect of Heated AB Serum on Leukocyte Chemotaxis

Six patients with a mean burn size of 50.0% total body surface burn (range 32–63%) and a mean functional chemotactic index of 70.6% (range 35.6-119%) demonstrated a significant ($P<0.05$) increase of functional

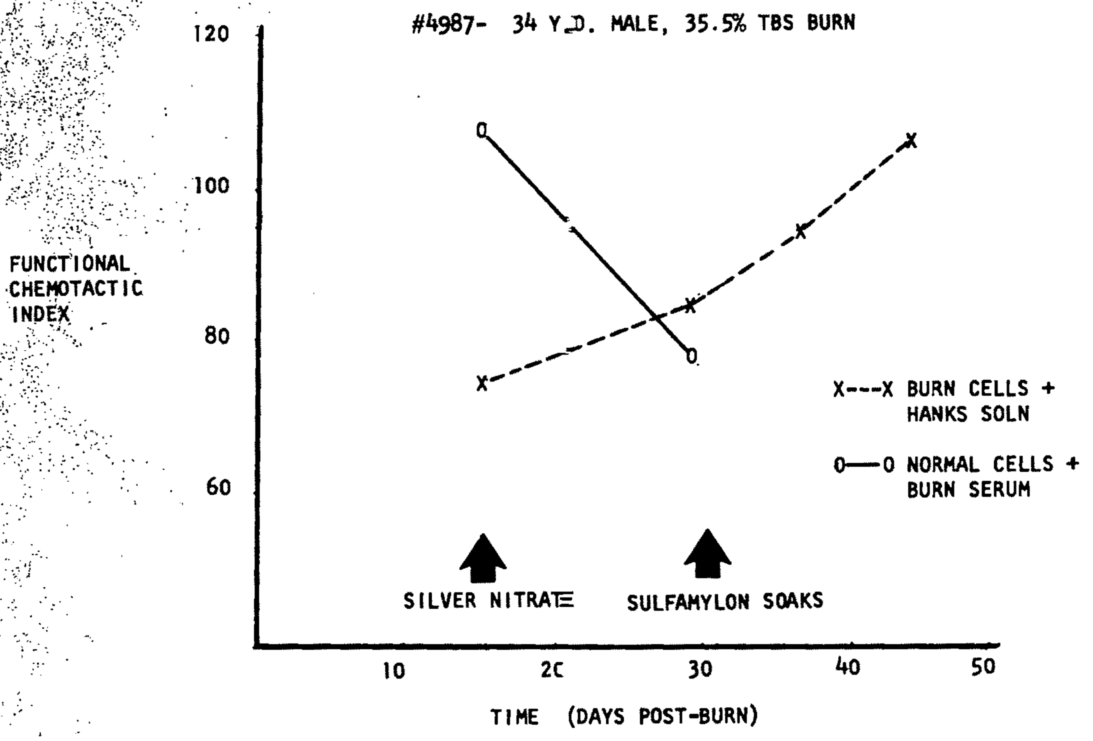

FIG. 5. Functional chemotactic index versus day postburn demonstrating suppression of normal leukocyte chemotaxis by burn serum after beginning mafenide acetate topical therapy.

chemotactic index (mean 102.6%; SE ± 3.25; range 93-115%) when their leukocyte rich suspension was incubated with normal type AB serum. However, when the normal type AB serum was heated for 20 minutes at 56 C, cooled at 37 C and then incubated with leukocyte rich suspension, there was no increase or decrease in the functional chemotactic index (mean 72.5%; range 41.3–106.7%) (Table 6). This experiment suggests that the factors in normal serum responsible for improving the chemotaxis of leukocytes from thermally injured patients are heat labile.

Effect of Albumin on Leukocyte Chemotaxis

Four patients with a mean burn size of 26.5% total body surface (range 20–30%) and a mean functional chemotactic index of 86.4% (range 44.9-119.4%) demonstrated no significant increase in leukocyte chemotaxis when their leukocytes were incubated with salt poor human albumin. The mean functional chemotactic index after incubation with salt poor albumin was 74.8% (range 35.3–111.2%). Although the albumin used was commercial salt poor albumin, this experiment suggests that the albumin fraction is not the active factor in normal serum responsible for increasing chemotaxis of leukocytes from thermally injured patients.

Discussion

Chemotaxis is an important biologic phenomenon determining the direction of motion of bacteria, plant and animal cells in reproduction, nutrition, cellular organization and inflammation. Various methods have been used to study chemotaxis but the method devised by Boyden in 1962[4] based on the ability of leukocytes to migrate through a filter toward a chemotactic agent, has been the most useful because of its simplicity and reproducibility. A number of modifications of this technic have been devised.[6,7,9] The importance of chemotaxis in the function of polymorphonucleocytes is demonstrated in Fig. 4 since even leukocytes fully capable of ingesting and killing microorganism are incapacitated if unable to sense and be directed towards the invading pathogen.

This study demonstrates 1) an intrinsic defect in the chemotaxis of leukocytes from burned patients and 2) suppression of the chemotaxis of normal leukocytes by serum from burned patients treated with either mafenide acetate or silver sulfadiazine.

Chemotaxis is suppressed soon after burn injury and this suppression is proportional to the extent of injury. That this suppression is not a drug effect is indicated: 1) by its occurrence in patients treated with silver nitrate; 2) by its reversal upon incubation with normal serum, an effect removed by heating the serum; and 3) by the failure of dilution alone to duplicate the effect of normal serum. In addition, the serum from one patient did not suppress the chemotaxis of normal cells during treatment with silver nitrate but inhibited such chemotaxis during treatment with sulfamylon soaks (Fig. 5). The chemotaxis of the patients' own cells was suppressed during both forms of treatment and subsequently returned to normal.

The effects of mafenide acetate and silver sulfadiazine upon normal leukocyte chemotaxis are readily demonstrated at concentrations which occur in serum during treatment. Silver nitrate does not exhibit such an effect in vitro.

Susceptibility to opportunistic freedom is a hallmark of burn injury. The etiology of this susceptibility is not understood, but one proposed explanation is failure of granulocyte defense. Others have demonstrated functional impairment of granulocytes from burned patients[1,2,5] and this study suggests that delivery of these impaired granulocytes may also be faulty. The study further suggests a dilemma: the use of either mafenide or silver sulfadiazine to protect the burn wound from infection may cause further suppression of the delivery of granulocytes and thereby enhance the susceptibility of the patient to infection by other routes. Such a hazard of therapy has not been examined previously and its importance is not defined at this time.

Incubation in normal serum restores chemotactic function to the granulocytes obtained from burned patients. This restoration of function appears due to a heat labile component of normal serum. If similar restoration of function can be achieved in vivo, this observation may have clinical importance, since such restoration would permit a direct test of the relationship between chemotactic suppression and susceptibility to opportunistic infection in burned patients.

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Acute Renal Insufficiency Complicating Major Cardiovascular Surgery

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Thirty-one patients underwent hemodialysis for renal failure as a complication of major cardiovascular surgery at the University of Minnesota (1968–1973). Only eight patients (26%) survived. A review of the literature shows that since the beginning of hemodialysis the mortality of those patients has not improved. Infection was the overwhelming cause of death. The infections were difficult to diagnosis because they were frequently associated with abdominal abscesses that were almost uniformly overlooked. Several possible ways of improving these patients survival are: 1) the use of early operative interventions of second look type; 2) improved hygenic measures in the care of these patients; 3) more selective antibiotic treatment based on frequent reculturing; and 4) daily short dialysis in association with hyperalimentation.

POSTOPERATIVE acute renal insufficiency (ARI) is a discouraging complication associated with a high mortality rate. Since the mid 1940s when clinical dialysis was introduced, there has been no appreciable change in the mortality in spite of improved techniques of dialysis and the development of better understanding of postoperative management (hyperalimentation, patient monitoring, and the use of more effective antibiotics).[2,3,10,11,17] The reason for this high mortality is not entirely understood, but underlying disease, gastrointestinal bleeding, and infections have all been evoked as explanations.[2,3,10,11,17]

Over the last six years, 1968–1973, 31 of our 358 dialysis patients were treated for acute renal failure following major cardiovascular surgery. This paper reports our efforts to elucidate pathogenetic factors in the continued high mortality of these patients in spite of intense hemodialysis.

Patient Material

Thirty-one patients (4 women, 27 men) dialyzed for acute renal failure following major cardiovascular surgery 1968–1973 were included. The mean age was 60 years with a range of 25–72 years. Eight patients (26%) survived. Five patients were operated elsewhere and referred here because of acute renal failure.

Methods

Analysis of Data

The clinical records of these patients were reviewed, the primary purpose being to tabulate factors that could conceivably have influenced the death rate:

1) Common demographic factors: Age, sex, preexisting disease.

2) Intraoperative factors: Type of operation, duration of operation, technical complications, and later reoperation.

3) Durational factors: Number of days from the operation until the onset of acute renal failure (immediate or delayed), the recovery of renal function or death.

4) Dialysis protocol: The frequency of dialysis, the mean degree of uremia before the first dialysis for subsequent dialysis.

5) Bacterial and fungal cultures: Urine, sputum, wound, and blood culture.

6) Failure of various other organ systems: Failure of the respiratory system was defined as a need for a respirator, a bilirubin over 5 mg% appearing later than the third day after operation was regarded as a symptom of liver failure; failure of the CNS was characterized by stupor and coma. Furthermore, myocardial infarction, with or without arrhythmias and cardiogenic shock were tabulated as signs of failure of the cardiovascular system. The occurrence of gastrointestinal hemorrhage and bowel perforations were also noted.

Due to the complicated courses manifested by these patients, a single cause of death could not always be determined for specific patients.

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TABLE 1. *Pre-existing Risk Factors Other Than Leading to Operation*

	Died No (%)	Survivors No (%)
Heart Disease	5 (21)	1 (12.5)
Lung Disease	3 (13)	1 (12.5)
Hypertension	1 (4)	2 (25)
Kidney Disease	1 (4)	
Diabetes	2 (9)	
Peptic Ulcer	1 (4)	
CVA	1 (4)	
None	9 (39)	4 (50)
Total	23	8

TABLE 2. *Operation*

	Total	Survivors
Abdominal Aortic Aneurysm Emergency	8	1
Abdominal Aortic Aneurysm Elective	6	1
Thoracic Aortic Aneurysm	1	1
Coronary Artery By Pass	2	1
Valve Operation	7	2
Coronary Artery By Pass & Valve	1	-
Cardiotomy	1	-
Porta-Cava Anastamosis	1	-
Aorta-Femoral Grafts	4	2

Treatment

A uniform approach to therapy has been in force during the six year study. Most of the patients received broad spectrum parenteral antiobiotics prophylactically after surgery, usually 4-12 gm Cefalotin, daily. Cardiac monitors, central venous pressure and intra-arterial catheters were frequently employed. Foley catheters were usually kept in the bladder throughout the course. When oliguria supervened, all patients received ethacrynic acid or high doses of furosemide and mannitol both as IV pulse doses and as continuous intravenous infusions. The latter, however, was discontinued after a few hours unless polyuria supervened. When respirators were required, the patients were intubated for one to five days after which tracheostomy was performed. Only volume cycled respirators were used.

Hemodialysis was instituted early and used daily or every other day. The patients were treated six hours with relatively high efficiency dialyzers. All dialyses were done with regional heparinization according to a method previously described.[8] Usually the patient's clotting time was maintained below 20 minutes. All patients received aluminum-hydroxide to prevent phosphate absorption and as prophylactic therapy against gastroduodenal ulceration. Anabolic steroids and multivitamins were also employed. Intravenous and oral hyper-alimentation were used as needed during the last 12 months of the study.

Results: Factors Influencing Survival

Demographic Factors: Eight Patients Survived and 23 Died

One fourth of the men and one fourth of the women survived. The mean age of both the survivors and of the non-survivors was 60 years. Pre-existing disease other than that leading to the orignial operation could not be used as a prognostic guide. Approximately 50% of both those who eventually died and those who lived, stated that they had been in good health until their initial operation. The other 50% showed a scattering of previous diseases, but no distinct pattern could be discerned (Table 1). Obviously demographic factors had no influence on survival.

Influence of Operations on Survival

The small number of patients in each sub group, according to type of cardiovascular surgery, makes it difficult to discern any difference in survival (Table 2). Of the aneurysm group three of 15 patients survived versus three of 11 with cardiac operations and two of four with aortofemoral bypass grafts. The one patients who received a porta-caval shunt died. Duration of operation, transfusions, and technical complications did not differ between the survivors and the patients who died (Table 3).

Reoperations

The three surviving patients who had a second operation received it before the onset of renal failure. The reason for reoperation was hemorrhage. Eleven of the 23 patients who ultimately died underwent reoperations before dialysis for clotted grafts (5), hemorrhage (2), colectomies (necrosis of colon) (2), embolectomy of the carotid artery (1), and a foreign body (1). All of these operations except one were performed within one or two days after the primary operation. The single exception was a patient who had colectomy six days after placement of a synthetic abdominal aortic graft.

Renal Failure

Renal failure occurred immediately after operation in all eight survivors and in 17 of the 23 patients who died. Six of

TABLE 3. *Complicating Intraoperative Factors*

	Dead (23)	Survived (8)
Duration Operation Hours	5.9 (3-10.5)	7.7 (3.5-12.0)
Transfusion 1st Operation Liters	4.7 (0-13.0)	4.5 (1.3-10.0)
Technical Complications During Operation	4/23 (17%)	2/8 (25%)
Reoperations*	11/23 (48%)	3/8 (38%)

*Excludes shunt operation and tracheostomies.

TABLE 4. *Degree of Uremia Before Dialysis*

	Dead mg/100 ml	Survivors mg/100 ml
BUN 1st Dialysis	140 (40-234)	133 (104-180)
Creatinine 1st Dialysis	8.1 (4.2-16)	11.3 (7.5-17)
BUN Subsequent Dialyses	100 (40-150)	98 (75-120)
Creatinine Subsequent Dialyses	6.5 (3.0-11.0)	7.9 (6-10)

Figures are mean ± ranges.

TABLE 5. *System Failure*

	Dead*	Survivors
Heart	7/20	1/8
Respiratory	12/20	3/8
Liver	8/20	0/8
CNS	14/20	2/8
Upper GI	2/20	0/8
Bowel Perforation	2/20	0/8

*Excludes three patients surviving less than a week.

the patients who ultimately died had a delayed type of renal failure. Consequently, the mean time from the operation to the first dialysis is shorter in the survivors (six days, range 3-10 days) than in the patients who died (ten days, range 2-31 days). There were obvious causes for renal failure in 50% of the patients who died; hypotension in four patients and sepsis in nine. Hypotension caused the renal failure in two of the eight surviving patients.

We attempted to study the relationship of Cephaloitin, gentamycin, and furosemide to the onset of renal failure, because these agents alone or in combination have been implicated as a cause of ARI. The complicated courses of our patients, however, made such an assessment impossible. The patients who died had received a mean of four (range 1-18) dialyses versus eight (range 1-18) for the survivors. Eight dead patients received only one dialysis versus two in the surviving group. The frequency of dialysis was one every 1.8 days in dying patients versus one every 1.9 days in survivors. The patients who survived required dialysis for a mean of 16 days (range 1-38). All surviving patients achieved creatinine levels below 2 mg per 100 ml. after operation and the first dialysis was performed ten days after the operation; thus, the mean dialysis duration was eight days (range 1-34). The mean BUN and creatinine before the first dialysis and the mean BUN and creatinine before subsequent dialyses are shown in Table 4. There is a tendency for the non-surviving patient to have a higher BUN but a lower creatinine, both before the first and subsequent dialysis which in all probability represents higher catabolism and thus higher urea production. Supporting this theory is the lower creatinine in this group and the shorter period between dialysis in the patients who died.

The major difference suggests that the patient who ultimately survives is the one who has immediate simple postoperative renal failure. If delayed renal failure occurs, some complications of the operation that mitigates against survival may be the precipitating factor. Furthermore, the higher BUN suggests that the patients who died had a complication increasing catabolism such as tissue necrosis and/or infection.

Infections

The major difference between the patients who died and those who survived was the occurrence of septicemia. None of the eight patients who survived had positive blood cultures though candida was cultured from two CVP catheters. In contrast, ten of the 23 patients who died had positive blood cultures while alive and another four had positive blood cultures at postmortem examinations. The organisms were gram negative bacteria in 13 and coagulase positive staphylococcus aureus in one. Candida was cultured in conjunction with a gram negative bacteria in one patient. The mean survival time in the patients with positive blood cultures, 25 days, compared to 13 in those who died with negative blood cultures. The mean time of the first positive blood culture was 15 days after the primary operation.

TABLE 6. *Cause of Death*

	Postmortem Exam performed (17 pat.)	No Postmortem Exam Performed (6 pat.)	Total
Infection:			
Source unknown	2	3	5
Retroperit. Absc.	6	1	7
Pyo-pericardium	2	-	2
All Infections:	10	4	14
Emboli	1	1	2
Myocardial Infarct	2		2
Heart Failure	1		1
Respiratory Insufficiency	1		1
Cerebral Hemorrhage	1		1
Technical	1	1	2
	17	6	23

Once a positive blood culture was obtained it usually persisted. In all patients the positive blood cultures were obtained in spite of intense broad spectrum antibiotic coverage. Of the ten patients who had positive blood cultures during life an abdominal abscess was present in four. The other six had no obvious source for the septicemia except positive urine and sputum cultures; however, postmortem examination was not performed in two patients.

In separately analyzing the non-surviving patients with abdominal aneurysms 10/12 had a postmortem examination performed. Seven of these ten patients had retroperitoneal abscesses. Four of these seven patients had positive blood cultures during life, another two had positive blood cultures at postmortem examination. The abscesses were diagnosed or suspected in only two before death. One patient had a laparotomy with drainage of an abscess (this patient died at surgery), the other patient died of disseminated intravascular coagulation before laparotomy could be performed.

Sputum and urine cultures were of little value as a prognostic aid or in ascertaining the etiology of the septic state.

Early in the postoperative course, both surviving and patients who later died had a conglomerate of gram negative rods. The urine cultures were less frequently positive than sputum in both groups. Once either sputum or urine became positive, they remained so. *Candida albicans* appeared in the sputum in one third of the surviving patients and in two thirds of the non-surviving patients. Candida was found in the urine of one-half of the surviving patients, and one third of the non-surviving patients. Hyperpyrexia (temperature over 102F) was also unreliable as an indicator of survival because it was absent in only two patients; one survived and the other patient, with a positive blood culture, died. Sequential cultures were not always obtained in this retrospective study, and it is possible that a more systematic method of culturing may lead to different conclusions.

Organ System Failure

The clinical appearance of organ system failure is shown in Table 5. The only clear difference between the patients who survived and those that died was that any who developed liver failure eventually died.

Causes of Death

Sixty per cent (14/23) of the deaths were caused by infections, even though sepsis was not suspected in the majority of these cases (Table 6).

Discussion

It is sobering to compare the result of our series to those reported since the early 1950s.[2,3,11,19] The mortality in post-surgical acute renal failure necessitating hemodialysis has remained almost unchanged, 60-70%, in spite of: 1) greatly improved techniques of hemodialysis; 2) small volume, high efficiency dialyzers; 3) ease of access to the blood stream through the use of shunts; 4) more intense dialysis; 5) the development of more efficient antibiotics; and 6) the increased use of hyperalimentation.

Both Stott[17] and Alwall and Kjellstrand[2] have shown a direct relationship between age and mortality. Most series also have shown a direct relationship between mortality and the nature of the illness that leads to ARI. One finding that all the reports have in common is that when acute renal insufficiency is of obstetric or gynecological origin, the prognosis is usually good. However, when ARI has developed following trauma or abdominal or cardiovascular surgery, the deaths have been uniformly high.[2,3,10,11,17,19]

In spite of what seems to be a fatal combination of old age and major operations, this series suggests that we still have to make every effort to save lives.

Only nine of our patients died of causes that we felt would have been difficult to influence once they were established. On the other hand, 14 of our patients died of infections. Alwall and Kjellstrand[2] made the same observations: 20% of their patients had peritonitis, 30% had septicemia, 56% had purulent bronchitis, and 79% showed bacteriuria. Infection was the leading cause of death in the series reported by Balslov et al.[3] and Stott et al.,[17] and Kleinknecht and coworkers.[11]

A recent paper reported different mechanisms of death in postoperative patients with ruptured abdominal aneurysms complicated by acute renal failure that required hemodialysis. The overwhelming pattern of death in their patients was sequential organ failure; pancreatitis was followed by failure of the lungs, liver, central nervous system, and of the gastrointestinal tract. Only one of their 18 patients survived.[19]

We could not, however, find a similar sequence of events in our patients. If these findings were general, obviously death would be unavoidable and these patients should not be treated with dialysis. Although the organ system of several of our patients showed evidence of failure only one, liver failure, seemed to be uniformly fatal. The reason for the discrepancy between our findings is not readily apparent. The number of patients, their age, their mode of arrival at the hospital, the pre-existence of systemic disease, and the mode of treatment with dialysis is almost identical in the group of patients at the Peter Bent Brigham Hospital[19] and our patients. Other series[2,3,10,11,17] likewise did not associate death with sequential organ failure in the majority of the patients.

There have been three suggested approaches to improving the discouraging results of older patients with ARI that have undergone prolonged traumatic surgery.

The very earliest suggestion was intensified hemodialysis. The earliest advocates of this,[13,16,18] however, reported the results of small, relatively unconvincing series. Balslov[3] and Kleinknecht[11] presented good evidence that delayed initiation of dialysis, combined with infrequent dialysis resulted in a higher mortality rate. These observations, however, came at a time when dramatic policy changes were being made. Instead of allowing the occurrence of severe uremia (BUN of 350), dialysis was instituted before the blood urea nitrogen had reached 100 mg per 100 ml. Since our patients were already being dialyzed approximately every other day, the only improvement would be to institute daily dialysis. Short daily dialysis may be advantageous. It has been shown[9] that cycling of body chemistries and water content by intermittent dialysis may be more detrimental than absolute levels of BUN, urea, and other uremic toxins.

The second method that could possibly improve the mortality of these patients is intravenous hyperalimentation.[1] However, intravenous hyperalimentation in these patients frequently causes complications namely, hyperglycemia, hyperosmolality, fluid overload, and is a potential source of sepsis and aggravating already present chemical abnormalities. Fluid overload and hyperglycemia have been the most difficult to control. Nevertheless, we have instituted a routine schedule of hyperalimentation because of the vicious cycle of starvation-infection as a cause of death in our patients. The results at present are inconclusive.

Early and aggressive operative intervention has also been suggested as a means to lower the mortality of these patients.[12] The old surgical axiom that devitalized, infected tissue must be removed if the patient is to survive was not followed in several of our patients. Two problems were encountered in this respect. One was the extreme difficulty in diagnosing retroperitoneal abcesses. High fever was present in all our patients and clinical examinations of the abdomen were difficult to interpret.

Diagnostic peritoneal lavage was infrequently used in this group of patients. As no patients developed an intra-abdominal abcess (the abscesses were retroperitoneal), the beneficial value of lavage may be limited. Echograms were not employed, although this relatively new tool may prove helpful and should be used. In the past there has been a reluctance to reoperate on these desperately ill patients. However, since no patients with septicemia and intra-abdominal abcesses have survived it seems that aggressive reoperations are a must to reduce the mortality of these patients. The delayed onset of renal failure always tokens a lethal complication when renal failure occurs soon after the first operation it is less lethal. Similarly, positive blood culture results suggests undrained septic focus, and at least daily blood cultures should be done.

Another approach would be to prevent the formation of retroperitoneal abscesses. All of the abscesses in our series were located in the hematoma in the retroperitoneal space and frequently incapsulated the synthetic grafts. A large retroperitoneal hematoma is always present in ruptured aortic aneurysms, and probably occurs to a lesser degree in elective graft replacement of lower abdominal aorta. The formation of abscesses and subsequent graft infections may be prevented or decreased by removing as much as possible of the clot.

One potential source of the gramnegative bacteria that infect the hematoma, may be the intraoperative bowel trauma (manipulation and placing the intestine in various bags to expose the aorta). Particularly during long procedures when the organisms could "leak" through the bowel wall and contaminate the retroperitoneal area. Preoperative reduction of the bowel colony count may influence this outcome. Experimental animals tolerate lethal forms of trauma better when the bacterial counts of the gut have been reduced.[15] Oral, non-absorbable antibiotics used to reduce intestinal bacteria, in combination with a protected environment has also shown to decrease the mortality of infectious complications of leukemia chemotherapy.[7] There was no correlation in our group of patients between reoperation and subsequent abscess formation. This does not mean that reoperation carries no morbidity, but in trying to find the etiology of abscess formation, reoperation did not seem to increase the infectious problems.

The final method that may improve mortality rates in this group of patients may be through intensified aseptic catheter and nursing care, thereby creating better prophylaxis of infections. Postoperative patients with ARF may be immunosuppressed as both major surgery and uremia are immunosuppressive.[6,14,20] Barrier nursing has been suggested to improve mortality in patients undergoing cancer chemotherapy.[4,5] We are impressed, however, that our patients uniformly died from infections that seemingly emanated from their own gastrointestinal flora. Strict isolation procedures on these patients who require intense nursing and physician supervision would be virtually impossible to accomplish. It has been suggested[4] that since the gram negative bacteria do appear in the sputum and urine, bactericidal soap and intense perineal care should be used to prevent their spread.[4] Similarly, the multiple catheters that are used in these patients may act as seeding sites for bacteria that will later lodge in hematomas and lead to abscess formation. Therefore, The Foley catheter should be removed when oliguric renal failure is established as it serves no useful purpose. Similarly, intra-arterial and intravenous catheters should be avoided. The Scribner Shunt serves as a convenient source of arterial blood and also can be used for long-term hyperalimentation. This shunt may, of course, also be a source of infection but with frequent dialysis it is unavoidable. Meticulous tracheostomy and catheter care with antibacterial ointments should be employed. Intensified culturing of sputum, wound, urine, and blood, followed by appropriate antibiotic changes, should also be used.

Stott and coworkers[17] have already pointed out that the patient with acute renal failure has had a tendency to be a "forgotten minority", with most of the interest of present day hemodialysis focused on the care of the patient with chronic renal failure. Although the patient with acute renal failure requires an enormous investment of money and time, this is only for a short period of time; and if the patient survives, he is usually self-supporting from then on. This is in contrast to the patient with chronic renal failure who will require a great investment for years or until successfully transplanted. In essence, a strong suspicion of the presence of an abscess, an aggressive attitude towards a "second look" procedure, strict aseptic care of catheters, hyperalimentation, and frequent dialysis may all favorably influence the outcome of these acute renal failure patients.

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Gastrocolic and Gastrojejunocolic Fistulae: Report of Twelve Cases and Review of the Literature

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Seven gastrocolic and five gastrojejunocolic fistulae were recorded at Charity Hospital between 1940 and 1970. Such fistulae occurred in males more often than females. In this series, as in others, the most common cause was gastric surgery for peptic ulcer disease. Pain, diarrhea, and weight loss were clinical findings in half the patients; anemia, leukocytosis, electrolyte disturbances and hypoalbuminemia were common laboratory findings. A fistula was demonstrated radiologically in nine of the twelve patients. Management of these patients included no operation (3); two-stage procedure (2); and one-stage procedure (7); with a recent trend toward the one-stage procedure. A case report of a fistula resulting from postoperative complications of perforative appendicitis in which a successful combination of hyperalimentation and diverting colostomy was used is presented.

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PRIOR to the advent of gastric surgery, direct communication between the stomach and the colon was usually secondary to cancer, syphilis, tuberculosis, or trauma. By 1900, there was only 90 cases reported in the literature. In the late 1800s, Wolfer and von Hacker devised the gastroenterostomy as treatment for ulcer disease. As early as 1903, Czerny defined a gastrojejunocolic fistula following gastroenterostomy.[22] Since then, the entity has become a well-defined clinical syndrome, and its etiology following gastroenterostomy recognized. With the advent of vagotomy and drainage, and higher gastrectomy, the incidence of marginal ulceration has been reduced considerably from the previous estimate of 15%.[10] The incidence of gastrocolic and gastrojejunocolic fistulae also should have declined, leaving the causes of fistulization to the spontaneous varieties seen early in this century.

This report details the experience of the Louisiana State University Department of Surgery in the care of 12 patients with gastrocolic and gastrojejunocolic fistulae at Charity Hospital in New Orleans as well as a review of the experience of others.

Results

The records of 12 patients treated for gastrocolic and gastrojejunocolic fistulae from 1940 through 1973 were reviewed. The clinical course, laboratory data, and management of these patients were evaluated.

The ages ranged from seven to 84 years, with a median of 52 years. There were eight males and four females. Seven patients had a gastrocolic fistula, and five had a gastrojejunocolic fistula.

The types and causes of gastrocolic and gastrojejunocolic fistulae are shown in Table 1. The etiologies of these fistulae were varied, the most common cause being gastric surgery for peptic ulcer disease.

Pain, diarrhea, and weight loss were the most common clinical findings in the 12 patients studied (Table 2). Malnutrition was the most common presenting sign. Only one patient presented with fecal vomiting, which usually is considered a classic symptom of this disease. Steatorrhea, postprandial pain, and heartburn were not present in any of these patients.

Laboratory findings included anemia, leukocytosis, electrolyte disturbances, and hypoalbuminemia in all. In this series, the hematocrit was less than 35% in half the patients, with a median of 35.7%.

Radiologic diagnosis of the fistula was made in nine of the 12 patients, five by barium enema, and two by upper gastrointestinal series. Two patients' fistulae were demonstrated by both barium enema and upper gastrointestinal series. Gastroscopy was performed in five patients,

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TABLE 1. *Gastrocolic and Gastrojejunocolic Fistulae at Charity Hospital in 12 Patients*

Type and Cause	
Gastrocolic	
Gastroenterostomy for peptic ulcer disease	2
Benign gastric ulcer (not operated)	1
Pancreatic abscess	1
Perforated appendix with subphrenic and lesser sac abscess	1
Perforated diverticulum	1
Unknown	1
Gastrojejunocolic	
Gastroenterostomy for peptic ulcer disease	3
Malignant disease of the colon	1
Regional enteritis	1

TABLE 2. *Clinical Findings in 12 Cases of Gastrocolic and Gastrojejunocolic Fistulae*

Pain	6
Weight Loss	6
Diarrhea	4
Malnutrition	4
Nausea	4
Anemia	3
Hematemsis	2
Abdominal mass	1
Constipation	1
Fecal Vomiting	1
Flatulence	1
Melena	1
Pain relieved by foods/antacids	1

but the fistula was demonstrated in only two. Colonscopy was not performed on any patient in this series.

The management of the 12 patients with gastrocolic and gastrojejunocolic fistulae (Table 3) included a one-stage procedure in seven. The only mortality, due to Candida sepsis, was in this group. Two patients had a two-stage procedure with neither complications nor mortality. Three patients were not operated upon.

Long term followup of the patients revealed that of the three patients who had no operations, two died of undetermined causes, and one was lost to followup. Of the nine remaining patients, three have been lost to follow-up. The remainder have been followed for periods ranging from six months to 17 years. The only one who continues to have problems is the patient with chronic inflammatory disease of the small bowel.

The following is a case report of an unusual gastrocolic fistula.

Case Report

A seven-year-old Negro male was admitted to Charity Hospital on October 11, 1972 with a two-day history of lower abdominal pain accompanied by nausea and vomiting. His past history included the usual childhood illnesses, but no previous operations.

On examination the child was found to be in no distress with normal vital signs for his age and a temperature of 38.4C. Pertinent physical findings were limited to the abdomen, which was rigid, diffusely tender, and had no bowel sounds.

Laboratory studies revealed a normal urinalysis, WBC count of 19,300 with a marked shift to the left, hematocrit of 40.4% and normal electrolytes. Chest and abdominal films were within normal limits.

A diagnosis of acute perforated appendicitis was made. The patient was started on parenteral antibiotics and taken to the operating room where he was found to have a free perforation of his appendix with generalized contamination of the abdominal cavity.

The patient's postoperative course was complicated by bilateral subphrenic abscesses, a cul-de-sac abscess, lesser sac abscess and multiple interloop abdominal abscesses requiring four different surgical drainage procedures.

In January, 1973, two and one-half months after admission to the hospital and six weeks after drainage of an interloop abscess, the patient continued to run a low-grade temperature, was losing weight, and in general was doing poorly. Intravenous hyperalimentation was begun and an upper gastrointestinal series and barium enema were obtained in an effort to demonstrate additional intra-abdominal abscesses. The upper gastrointestinal series was within normal limits, but the barium enema demonstrated a small gastrocolic fistula between the stomach and the midtransverse colon. Hyperalimentation was continued for an additional two weeks at which time the patient underwent a right transverse colostomy. He did well postoperatively and was discharged on the 10th postoperative day, afebrile and gaining weight.

In June, 1973 barium enema showed no abnormalities with apparent closure of the gastrocolic fistula. His colostomy was closed and he has continued to do well and is free of complications.

Discussion

Gastrocolic and gastrojejunocolic fistulae have enough in common in the clinical presentation and diagnosis that they can be discussed together. However, their incidence and etiology differ so that a distinction between the two must be made. The forerunner to the development of a gastrojejunocolic fistula is the marginal ulcer, and as long as marginal ulcers exist, an occasional fistula will develop. Marshall reported that one out of seven individuals with marginal ulceration develops a gastrojejunocolic fistula. In his own series of 257 jejunal ulcers, 49 developed fistulae, an incidence of 18%.[16] A report from the Henry Ford Hospital in Detroit showed that in 81 diagnosed marginal ulcers, seven fistulae developed, an incidence of 8.6%.[1] In our own series, four of five gastrojejunocolic fistulae occurred due to marginal ulcer after gastroenterostomy, but an accurate appraisal of the number of marginal ulcers is not available. A significant question to be considered is whether or not the incidence of gastrojejunocolic fistula has changed significantly since surgery for peptic ulcer has become more aggressive. This question apparently cannot be answered completely as yet. Although the incidence of marginal ulcer is suggested to have fallen since the addition of vagotomy and resection to the treatment of peptic ulcer, not enough cases have been reported to make a definite statement. However, Hardy states that the series reporting the usual ⅔ distal gastric resection have an incidence of marginal ulcer of less than 5% as compared to the incidence of 15% following gastroenterostomy alone.[2]

TABLE 3. *Management and Results of Gastrocolic and Gastrojejunocolic Fistulae at Charity Hospital of Louisiana*

Sex	Age	Etiology	Type of Fistula	Operative Procedure	Outcome
M	7	perforated appendix and intra-abdominal abscess	gastrocolic	colostomy, hyperalimentation, colostomy closure (II stage)	2 years postop., doing well
M	70	gastroenterostomy for peptic ulcer disease	gastrocolic	gastrectomy, colectomy, (I stage)	2 months postop., doing well
F	46	pancreatic abscess	gastrocolic	gastrectomy, colectomy, (I stage)	died 15 days postop. from intra-abdominal abscess—Candida sepsis
F	71	perforated diverticulum	gastrocolic	colostomy, gastrostomy, colectomy, colostomy closure ((II stage)	lost to followup
M	55	postop. gastric surgery for peptic ulcer disease	gastrocolic	none	died, cause unknown
M	53	recurrent ulcer disease. (not operated)	gastrocolic	none	died, cause unknown
M	84	unknown	gastrocolic	none	lost to followup
F	29	recurrent regional enteritis	gastrojejunocolic	resection of fistula and ileocolostomy	continued to have problems with primary disease
M	53	malignant disease of colon	gastrojejunocolic	gastrectomy, colectomy, resection jejunum (I stage)	1 year postop., gaining weight asymptomatic
M	44	postop. gastric surgery for peptic ulcer disease	gastrojejunocolic	gastrectomy, colectomy, resection jejunum (I stage)	asymptomatic, 17 years postop.
F	62	postop. gastric surgery for peptic ulcer disease	gastrojejunocolic	revisionary gastroenterostomy, colectomy, resection jejunum (I stage)	lost to followup
M	48	postop. gastric surgery for peptic ulcer disease	gastrojejunocolic	revisionary gastroenterostomy, colectomy, resection jejunum (I stage)	lost to followup

The exact incidence of gastrocolic fistula cannot be tabulated, but it remains a rarity. Carcinoma of the stomach or colon remain the commonest causes of such fistulae. In a large series from the Lahey Clinic where a combined total of 4700 cases of carcinoma of the stomach and colon were reviewed, 11 fistulae were found.[16] In a review spanning 51 years from the Mayo Clinic, Smith et al. found 29 cases, 12 of which were associated with carcinoma of the stomach, and the remaining 17, with carcinoma of the colon.[20] These, along with 167 cases reported by MacMahon and Lund, represent the majority of cases reported in the literature.[15]

Trauma, intra-abdominal abscess, tuberculosis, syphilis, ulcerative colitis, and unusual causes as that occurring as a complication of gastrostomy reported by Cook, have been reported.[6] Of particular interest, however, is the recognition of benign gastric ulcer as a cause of gastrocolic fistulae. Firth reported the first case of gastrocolic fistula secondary to benign gastric ulcer in 1920. Miller and Delaney reported 15 cases they had found in the world literature, and added one case of their own.[17] We were able to find an additional 8 cases in the literature plus one case of our own—reported by Ganji et al—in 1967.[8] This brings the total now to 25 cases with 18 being reported since 1964.[5,7,9,11,13,18,23] Benign gastric ulcer has become a prime differential in the diagnosis of gastrocolic fistula.

The end result of such a communication in the alimentary tract can become a devastating syndrome, manifested by weight loss, anemia, and severe diarrhea with fecal vomiting. The mechanism of this syndrome was uncertain until Kiskaddon, Templeton, and Renshaw reported an extensive experimental and clinical investigation to document the pathogenesis of this syndrome.[12] They concluded that deranged digestive and absorptive functions of the small intestine, caused by the regurgitation of colonic contents through the fistula into the stomach, bring about the syndrome. Damage occurs by transit of fecal material through the small intestine.

The diagnosis of gastrocolic or gastrojejunocolic fistula is not a difficult one and can often be made on the basis of history and physical examination alone. The majority of these patients will present with the classic symptoms of diarrhea, weight loss and feculent vomiting, and in the case of gastrojejunocolic fistula will usually have some previous history of peptic ulcer disease and gastric surgery. Most will present a picture of severe malnutrition with dehydration and electrolyte imbalance.

Laboratory findings usually reflect a severe state of malnutrition and dehydration with electrolyte imbalance, diminished serum proteins and vitamin deficiencies. A slight leukocytosis may be present as well as a mild to moderate anemia which may be observed because of hemoconcentration. Gastric acidity has been shown to be of little value; however, the quality of nasogastric aspiration may be significant if fecal material is aspirated.

The most reliable diagnostic aid in establishing this diagnosis is the barium enema. In 1960, Thoeny, Hodgson and Scudamore studied 66 gastrojejunocolic or gastrocolic fistulae in 65 patients and found that barium enema was the most accurate roentgenologic means of diagnosis.[21] They reported a 95% success rate with barium enema as opposed to only 27% with upper gastrointestinal series in both types of fistulae.

Other diagnostic aids such as gastroscopy and colonoscopy have not thus far been proven to be as beneficial diagnostically. However, with recent advances in technology and more experienced endoscopists, these procedures should be considered in the preoperative evaluation of these patients. Other simple diagnostic aids may be of some benefit. Once such test involves placement of a nasogastric tube, followed by a high enema of tap water with indigo carmin. The nasogastric aspirant is then observed for presence of the dye, and if positive indicates a communication between the stomach and colon.[19]

Because of the debilitating nature of gastrocolic and gastrojejunocolic fistulae, careful clinical and laboratory evaluation must be carried out in the preoperative period. Many of these patients are malnourished, anemic, and in electrolyte imbalance. In a series of cases reported from the Mayo Clinic over 50% of patients were noted to have clinical evidence of avitaminosis.[3] These conditions should be corrected as nearly as possible preoperatively. An important adjunct to the management of these patients is intravenous hyperalimentation. This is an excellent method of replacing deficiencies in calories, protein, and vitamins in the debilitated patient, particularly those who cannot tolerate oral feedings.

In addition to the case reported here in which a gastrocolic fistula was managed by diverting colostomy and hyperalimentation, a case managed in a similar manner was reported by Miller.[17] In that case the fistula also closed after the diverting colostomy was created and hyperalimentation utilized. However, definitive surgery was subsequently carried out in this patient for correction of his ulcer diathesis. Perhaps this method of management should be considered in selected cases, thus obviating the need for extensive surgical procedures in some patients.

Systemic antibiotics are usually not needed in the preparation of the patient unless a concomitant infection is present. However, oral antibiotics are usually administered for the purpose of bowel preparation prior to surgery. In our institution oral kanamycin with laxatives and cleansing enemas is used for preparing the colon for surgery.

Over the years the surgical management of gastrocolic and gastrojujunocolic fistulae has varied a great deal, ranging from simple colostomy to three-stage procedures consisting of colostomy followed by resection of the fistula, followed by closure of the colostomy. As was stated earlier, the mechanism of this syndrome is the transit of fecal material through the small intestine with subsequent derangement of digestive and absorptive functions.

It should be noted that all of these procedures have one thing in common—the diversion of the fecal stream away from the upper gastrointestinal tract, which allows the small intestine to function normally. This makes these procedures beneficial in the management of gastrocolic and gastrojejunocolic fistulae. Prior to the 1930s treatment generally consisted of resection of the fistula without attempts at correction of the ulcer diathesis. Recurrence rates of ulcer and/or fistula were high. Localio, Stone and Hinton reviewed 115 cases between 1943 and 1953 and found a recurrence rate of 50% among those treated with resection of the fistula as compared with 4% among those treated with correction of the ulcer diathesis.[14]

In the late 1930s defunctionalizing colostomies and staged operative procedures became popular in the treatment of fistulae of either benign or malignant origin. Pfeiffer and Kent proposed the simplest of these which was a three-stage procedure consisting of: 1) colostomy 2) resection of the fistula; and 3) closure of colostomy. The obvious disadvantage to this is that three major surgical procedures are required. Lahey in 1938 proposed a two-stage procedure consisting of a proximal defunctionalizing ileosigmoidostomy followed by resection of the fistula, subtotal gastrectomy and colectomy, thus obviating the need for a third-stage, colostomy closure.[16] This procedure also had other advantages such as maintenance of bowel continuity as well as absence of skin contamination and lack of fixation of the hepatic flexure. This procedure significantly reduced the mortality and morbidity in the treatment of this disease and was generally accepted as the procedure of choice.

Despite the advantages of Lahey's procedure and the significant reduction in the mortality and morbidity, steady advances in pre- and postoperative care during the 1940's made the one-stage procedure with correction of the fistula and ulcer diathesis seem more feasible. With progress in antibiotic therapy, blood replacement and a greater knowledge of electrolyte balance, the mortality and morbidity of such extensive procedures was significantly reduced. Barber, Waugh, and Priestly reviewed 76 patients who underwent one stage procedures from 1941 to 1960 for gastrojejunocolic fistulae due to peptic ulcer disease.[4] Sixty-three of these patients were followed up to five years. The mortality rate was 2.6% and there were three recurrences for a rate of 4.3%. There are several smaller series studied with similarly good results. Marshall et al. pointed out the steady decline in operative mortality, from 25% in 1927–1936 to 4% in 1937–1946 when the two-stage procedure was commonly employed, to no deaths from 1947-1955 when the one stage procedure was performed in 18 cases.[16]

Data available at the present time seem to indicate that the one-stage procedure consisting of resection of the fistula, colectomy, and subtotal gastrectomy is feasible in selected patients with gastrocolic or gastrojejunocolic fistulae.

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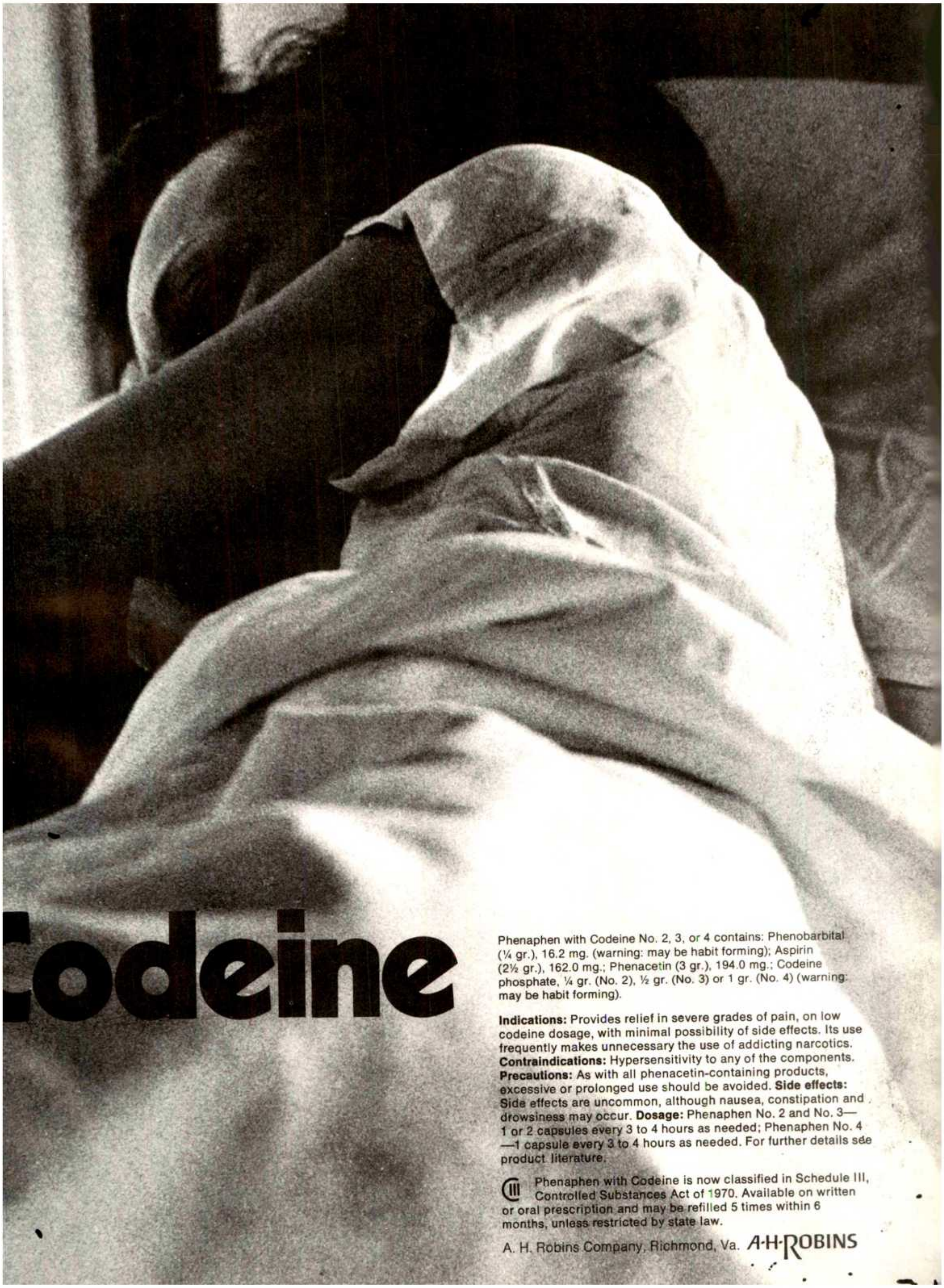

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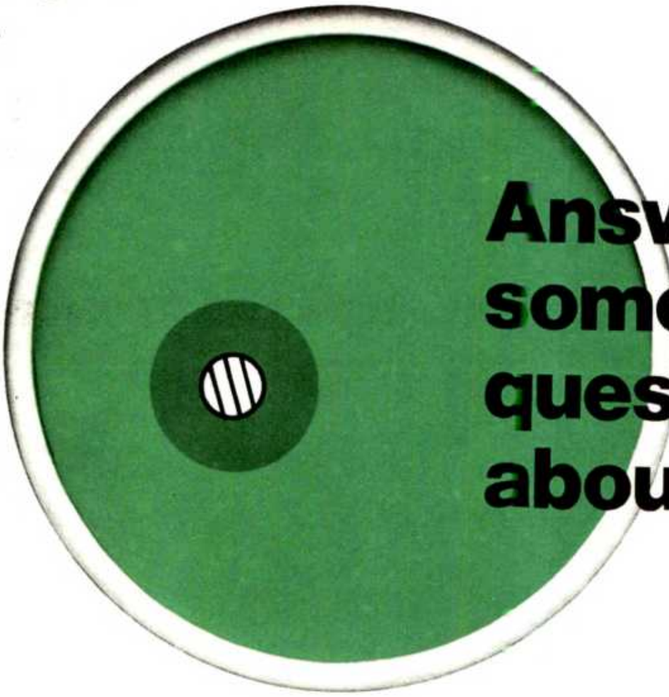

Answers to some important questions about resistance

Q: What is the nature of bacterial resistance to GARAMYCIN (gentamicin sulfate)?

A: Resistance has been shown, in the laboratory, to develop slowly in stepwise fashion. No one-step mutations to high resistance have been reported to date.

Q: What has been the experience concerning the potential for resistance to gentamicin?

A: After a year of isolating urinary tract pathogens in the laboratory of a 15-physician group practice in order to tabulate antibiotic resistance, Bauer[1] reported that common uropathogens were highly susceptible to gentamicin. Discussing their ongoing computerized studies of *in vitro* susceptibility of clinical isolates, Truant and co-workers[2] noted that gentamicin was the most effective *in vitro* of the chemotherapeutic agents they were employing. In a survey of the published studies on resistance to gentamicin, Weinstein and co-workers[3] found little change from 1963 to 1970 in the relatively high percentage of bacterial strains sensitive to gentamicin. *In vitro* sensitivity was determined in all cases by the tube-dilution method.

Q: Are gentamicin-resistant mutants of medical significance?

A: A laboratory study of strains resistant to gentamicin *in vitro* suggests that mutants that are gentamicin-resistant "...are probably of negligible medical significance," according to Weinstein and co-workers.[3] This is because the mutants were found to need exceptionally good conditions for growth and were rather unstable genetically. Accordingly, "These characteristics result in competitive disadvantages for these strains under natural conditions...."[3]

WARNING

Patients treated with GARAMYCIN Injectable should be under close clinical observation because of the potential toxicity associated with the use of this drug.

Ototoxicity, both vestibular and auditory, can occur in patients, primarily those with pre-existing renal damage, treated with GARAMYCIN Injectable, usually for longer periods or with higher doses than recommended.

GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

In event of overdose or toxic reactions, peritoneal dialysis or hemodialysis will aid in removal of gentamicin from the blood.

Serum concentrations should be monitored when feasible and prolonged concentrations above 12 mcg./ml. should be avoided.

Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

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Q: Has there been any change over the past four years in the *in vitro* susceptibility of major gram-negative pathogens to GARAMYCIN Injectable?

A: Gram-negative pathogens, recently identified and tested, demonstrated high susceptibility (96 per cent) to GARAMYCIN. From 1970 through 1973, there was virtually no decrease in the percentage of strains of major gram-negative pathogens susceptible to GARAMYCIN.

***In Vitro* Pathogen Susceptibility to Gentamicin, 1970-'73**

	1970	1971	1972-'73
Gram-negative Susceptibility	**97%**	**97%**	**96%**
No. of patient tests	**9,007***	**12,507***	**4,642****
Escherichia coli	97%	98%	98%
Proteus species, indole-negative	98	99	97
Proteus species, indole-positive	98	96	96
Pseudomonas aeruginosa	95	95	94
Klebsiella-Enterobacter-Serratia	100	100	98
Klebsiella pneumoniae	100	100	98
Klebsiella, all others	97	99	98
Gram-positive Susceptibility			
No. of patient tests	**2,698***	**2,962***	**1,122****
Staphylococcus aureus	96%	95%	95%

Source: I.M.S. Audit of Pathology Cultures, 1970-'73. These *in vitro* data are based on results obtained from hospitals in a nationwide audit. (*represents sample data from over 100 hospitals; **represents projections based on sample data from over 200 hospitals—add 000). The pathogens tested were obtained from all inpatient and outpatient services.

In vitro susceptibility data are not necessarily indicative of clinical effectiveness.

Q: Is R factor-determined resistance to gentamicin a clinical problem?

A: Very few problems have occurred to date with R factor-determined resistance to gentamicin. In all cases, this resistance has been controlled. In one clinical emergence in the United States, a resistant strain of *Klebsiella pneumoniae* was identified that caused an outbreak of infections at a Washington, D.C. hospital. Control measures were instituted, including a ban on the use of topical gentamicin and revision of hospital antiseptic procedures and "despite continued parenteral usage of gentamicin, the outbreak was successfully suppressed."[4]

Q: What has been the pattern of resistance to GARAMYCIN Injectable over an eight-year period (1963-1971) in investigational and clinical use?

A: One investigator noted: "In the experience so far with [gentamicin], which is 7 or 8 years, in centers where it's been restricted to parenteral use, resistance has not appreciably changed."[5] Another authority[6] "...found very little emergence of resistance..." during eight years of use.

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GARAMYCIN Injectable is potentially nephrotoxic, and this should be kept in mind when it is used in patients with pre-existing renal impairment.

Monitoring of renal and eighth nerve function is recommended during therapy of patients with known impairment of renal function. This testing is also recommended in patients with normal renal function at onset of therapy who develop evidence of nitrogen retention (increasing BUN, NPN, creatinine or oliguria). Evidence of ototoxicity requires dosage adjustments or discontinuance of the drug.

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Concurrent use of other neurotoxic and/or nephrotoxic drugs, particularly streptomycin, neomycin, kanamycin, cephaloridine, viomycin, polymyxin B, and polymyxin E (colistin), should be avoided.

The concurrent use of gentamicin with potent diuretics should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may cause a rise in gentamicin serum level and potentiate neurotoxicity.

USAGE IN PREGNANCY Safety for use in pregnancy has not been established.

INDICATIONS GARAMYCIN Injectable is indicated, with due regard for relative toxicity of antibiotics, in the treatment of serious infections caused by susceptible strains of the following microorganisms:

Pseudomonas aeruginosa, Proteus species (indole-positive and indole-negative), *Escherichia coli* and *Klebsiella-Enterobacter-Serratia* species.

Clinical studies have shown GARAMYCIN Injectable to be effective in septicemia and serious infections of the central nervous system (meningitis), urinary tract, respiratory tract, gastrointestinal tract, skin and soft tissue (including burns).

Bacteriologic tests to determine the causative organisms and their susceptibility to gentamicin should be performed.

Bacterial resistance to gentamicin develops slowly in stepwise fashion; there have been no one-step mutations to high resistance.

In suspected or documented gram-negative sepsis, GARAMYCIN may be considered as initial therapy. The decision to continue therapy with this drug should be based on the results of susceptibility tests, the severity of the infection, and the important additional concepts contained in the Warning Box.

For suspected sepsis when the infecting organism is unknown, gentamicin may be administered in conjunction with a penicillin-type drug. Following identification of the organism and its susceptibility, appropriate antibiotic therapy should then be continued. In the neonate with suspected sepsis or staphylococcal pneumonia, a penicillin-type drug is also usually indicated as concomitant therapy with gentamicin.

GARAMYCIN Injectable has been shown to be effective in serious staphylococcal infections. It may be considered in those infections when penicillins or other less potentially toxic drugs are contraindicated and bacterial susceptibility testing and clinical judgment indicate its use.

CONTRAINDICATIONS A history of hypersensitivity to gentamicin is a contraindication to its use.

WARNINGS See Warning Box.

PRECAUTIONS Neuromuscular blockade and respiratory paralysis have been reported in the cat receiving high doses (40 mg./kg.) of gentamicin. The possibility of these phenomena occurring in man should be considered if gentamicin is administered to patients receiving neuromuscular blocking agents such as succinylcholine and tubocurarine.

Treatment with gentamicin may result in overgrowth of nonsusceptible organisms. If this occurs, appropriate therapy is indicated.

ADVERSE REACTIONS

Nephrotoxicity: Adverse renal effects, as demonstrated by rising BUN, NPN, serum creatinine and oliguria, have been reported. They occur more frequently in patients with a history of renal impairment treated with larger than recommended dosage.

Neurotoxicity: Adverse effects on both vestibular and auditory branches of the eighth nerve have been reported in patients on high dosage and/or prolonged therapy. Symptoms include dizziness, vertigo, tinnitus, roaring in the ears and hearing loss.

Numbness, skin tingling, muscle twitching, and convulsions have also been reported.

Note: The risk of toxic reactions is low in patients with normal renal function who do not receive GARAMYCIN Injectable at higher doses or for longer periods of time than recommended.

Other reported adverse reactions, possibly related to gentamicin, include increased serum transaminase (SGOT, SGPT), increased serum bilirubin, transient hepatomegaly, decreased serum calcium; splenomegaly, anemia, increased and decreased reticulocyte counts, granulocytopenia, thrombocytopenia, purpura; fever, rash, itching, urticaria, generalized burning, joint pain, laryngeal edema; nausea, vomiting, headache, increased salivation, lethargy and decreased appetite, weight loss, pulmonary fibrosis, hypotension and hypertension.

DOSAGE AND ADMINISTRATION

GARAMYCIN Injectable may be given intramuscularly or intravenously.

For Intramuscular Administration:

*Patients with normal renal function**

Adults: The recommended dosage for GARAMYCIN Injectable for patients with serious infections and normal renal function is 3 mg./kg./day, administered in three equal doses every 8 hours.

For patients weighing over 60 kg. (132 lbs.), the usual dosage is 80 mg. (2 ml.) three times daily. For patients weighing 60 kg. (132 lb.) or less, the usual dosage is 60 mg. (1.5 ml.) three times daily.

In patients with life-threatening infections, dosages up to 5 mg./kg./day may be administered in three or four equal doses. This dosage should be reduced to 3 mg./kg./day as soon as clinically indicated.

**In children and infants, the newborn, and patients with impaired renal function, dosage must be adjusted in accordance with instructions set forth in the Package Insert.*

For Intravenous Administration:

The intravenous administration of GARAMYCIN Injectable is recommended in those circumstances when the intramuscular route is not feasible (e.g., patients in shock, with hematologic disorders, with severe burns, or with reduced muscle mass).

For intravenous administration, in adults, a single dose of GARAMYCIN Injectable may be diluted in 100 or 200 ml. of sterile normal saline or in a sterile solution of dextrose 5% in water; in infants and children, the volume of diluent should be less. The concentration of gentamicin in solution in both instances should normally not exceed 1 mg./ml. (0.1%). The solution is infused over a period of 1 to 2 hours.

The recommended dose for intravenous administration is identical to that recommended for intramuscular use.

GARAMYCIN Injectable should not be physically premixed with other drugs, but should be administered separately in accordance with the recommended route of administration and dosage schedule.

HOW SUPPLIED GARAMYCIN Injectable, 40 mg. per ml., 2 ml. multiple-dose vials for parenteral administration.

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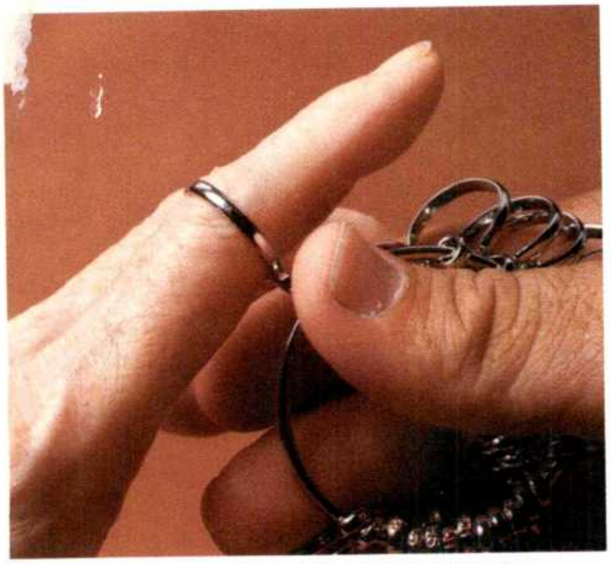

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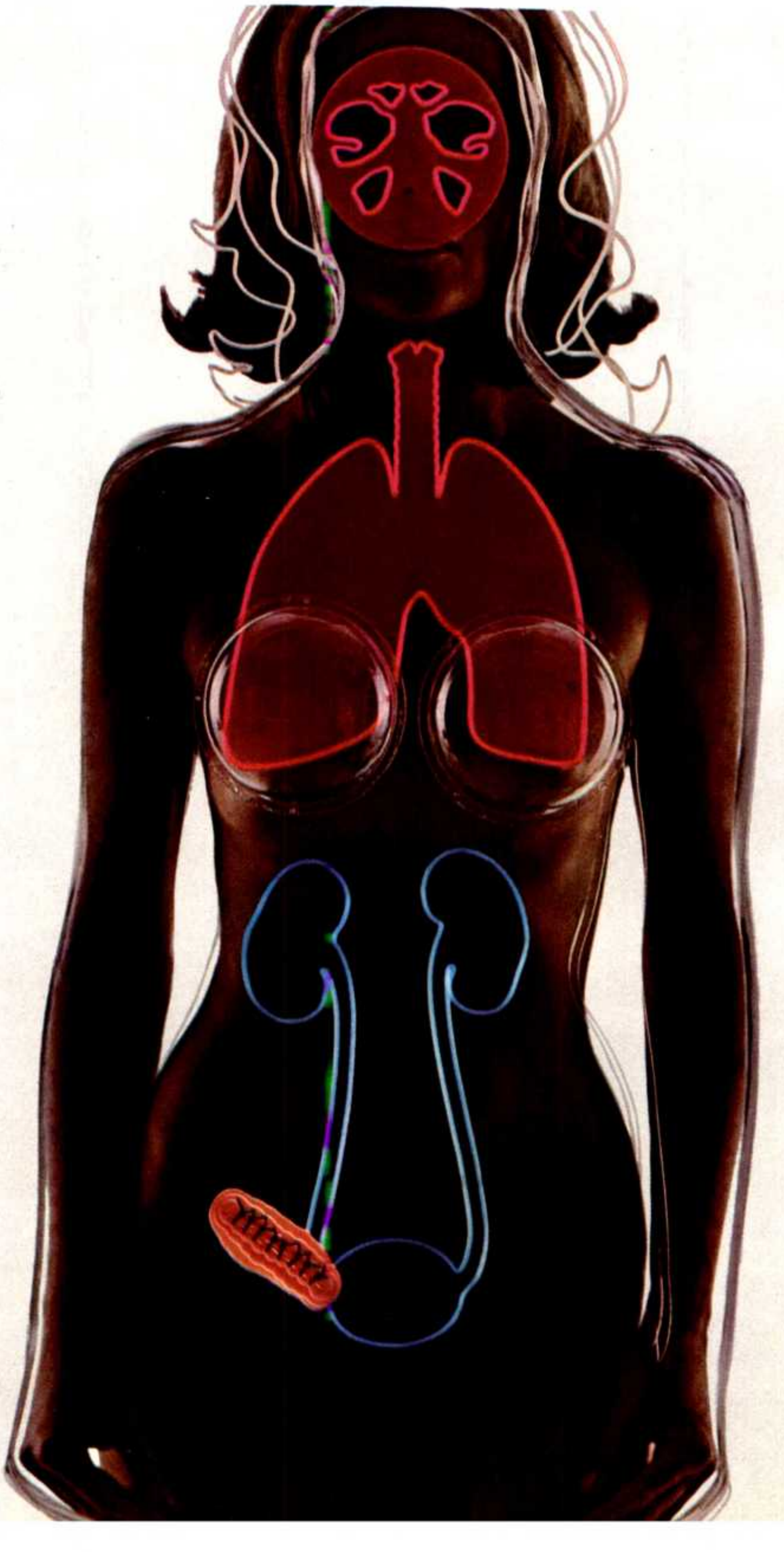
the Maalox®-protected aspirin

RORER

WILLIAM H. RORER, INC.
Fort Washington, Pa. 19034

New
from
SK&F

ANSPOR
BRAND OF
CEPHRADINE
capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.



SK&F
SMITH KLINE
& FRENCH
LABORATORIES

A New Oral Antibiotic with these Important Features:

- **Bactericidal activity *in vitro*.**
- **Effective against a wide range of Gram-positive and Gram-negative infections due to susceptible organisms:**

Respiratory tract infections caused by group A beta-hemolytic streptococci and *D. pneumoniae.*

Urinary tract infections caused by *E. coli, Pr. mirabilis,* and *Klebsiella* species.

Skin and soft-tissue infections caused by staphylococci.

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae, H. influenzae* and staphylococci.

Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

- **Documented safety.**
- **Rapidly absorbed. Average peak serum levels within 1 hour.**

(Approximately 9 and 16.5 mcg./ml. at 1 hour with 250 and 500 mg. capsules, respectively, in normal adult volunteers.)

- **High urinary levels.**

(Peak concentration of approximately 3200 mcg./ml. with 500 mg. capsule dose in normal adult volunteers.)

- **Excreted essentially unchanged in the urine.**
- **Acid stable. Can be given without regard to meals.**

'Anspor' is contraindicated in patients with known hypersensitivity to the cephalosporins. **In penicillin-sensitive patients, cephalosporin C derivatives should be used with great caution because of evidence of partial cross-allergenicity of the penicillins and the cephalosporins.**

Adverse Reactions

The following adverse reactions have been reported: glossitis, nausea, vomiting, diarrhea or loose stools, abdominal pain and heartburn; mild urticaria or skin rash, pruritus, joint pains; transient eosinophilia, leukopenia, neutropenia; transient rise of SGOT, SGPT, total bilirubin, BUN; dizziness, tightness in the chest, and candidal vaginitis.

For a brief summary of prescribing information, including indications, contraindications, warnings, precautions, adverse reactions, and dosage, please see the following page.

New from SK&F

ANSPO

BRAND OF
CEPHRADINE

capsules: 250 and 500 mg.
for oral suspension: 125 and 250 mg./5 ml.

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

DESCRIPTION

Anspor (cephradine, SK&F) is a semi-synthetic cephalosporin antibiotic chemically designated as 7-[D-2-amino-2-(1,4-cyclohexadien-1-yl) acetamido]-3-methyl-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid.

ACTIONS

Microbiology: *In vitro* tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Cephradine is active against the following organisms *in vitro*:

Beta-hemolytic streptococci
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains

Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella sp.
Hemophilus influenzae

Note—Some strains of enterococci (*Streptococcus faecalis*) are resistant to cephradine. It is not active against most strains of *Enterobacter* sp., *Pr. morganii* and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by *in vitro* methods, staphylococci exhibit cross-resistance between cephradine and methicillin-type antibiotics.

INDICATIONS

Anspor (cephradine, SK&F) is indicated in the treatment of the following infections when caused by susceptible strains of designated micro-organisms.

Infections of the respiratory tract (e.g., tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and *D. pneumoniae*.

(Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. 'Anspor' is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of 'Anspor' in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media caused by group A beta-hemolytic streptococci, *D. pneumoniae*, *Hemophilus influenzae* and staphylococci.

Infections of the skin and soft tissues caused by staphylococci.

Infections of the urinary tract, including prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* species.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

CONTRAINDICATIONS

Anspor (cephradine, SK&F) is contraindicated in patients with known hypersensitivity to the cephalosporin group of antibiotics.

WARNINGS

IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN C DERIVATIVES SHOULD BE USED WITH GREAT CAUTION. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES OF PATIENTS WHO HAVE HAD REACTIONS TO BOTH DRUGS (INCLUDING FATAL ANAPHYLAXIS AFTER PARENTERAL USE).

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously and then only when absolutely necessary.

Usage in Pregnancy and Lactation: Safety of this product for use in pregnancy has not been established. Cephradine is secreted in breast milk during lactation.

PRECAUTIONS

Follow patients closely to detect side effects or unusual manifestations of drug idiosyncrasy. If hypersensitivity reaction occurs, discontinue drug and treat patient with usual agents, e.g., pressor amines, antihistamines, or corticosteroids.

Administer with caution in presence of markedly impaired renal fun
In known or suspected renal impairment, careful clinical observatio
appropriate laboratory studies should be made prior to and during therapy as cephradine accumulates in the serum and tissues. See D
AND ADMINISTRATION section for information on treatment of patie
with impaired renal function.

Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms. Take appropriate measures if superinfection occurs during therapy.

After cephradine therapy, a false positive reaction for glucose in the
may occur with Benedict's solution, Fehling's solution, or with Clinit
tablets, but not with enzyme-based tests such as Clinistix* and Tes-

A positive Coombs test may be due to the drug.

Indicated surgical procedures should be performed in conjunction wi
antibiotic therapy.

ADVERSE REACTIONS

The following adverse reactions have been reported:

Gastrointestinal: Glossitis, nausea, vomiting, diarrhea or loose stool
abdominal pain and heartburn.

Skin and Hypersensitivity Reactions: Mild urticaria or skin rash, pru
and joint pains.

Blood: Mild, transient eosinophilia, leukopenia and neutropenia.

Liver: Transient mild rise of SGOT, SGPT, and total bilirubin with no evidence of hepatocellular damage.

Renal: Transitory rises in BUN. In adults for whom serum creatinine determinations were performed, the rise in BUN was not accompani
by a rise in serum creatinine.

Other adverse reactions have included dizziness and tightness in the
and candidal vaginitis.

DOSAGE AND ADMINISTRATION

Anspor (cephradine, SK&F) may be given without regard to meals.

Adults: For skin and soft-tissue and respiratory tract infections (other than lobar pneumonia), the usual dose is 250 mg. q.i.d. in equally sp
doses. For acute infections of the urinary tract, including prostatitis, a
pneumococcal lobar pneumonia, the usual dose is 500 mg. q.i.d. in equally spaced doses; severe or chronic infections may require larger doses.

Children: The usual dose is 25 to 50 mg./kg./day total, q.i.d. in equal
divided and spaced doses. For otitis media due to *H. influenzae*, doses
75 to 100 mg./kg./day in equally divided and spaced doses are recom
mended. Maximum dose should not exceed 4 grams per day.

All patients, regardless of age and weight: Larger doses (up to 1 gram
q.i.d.) may be given for severe or chronic infections.

In patients with impaired renal function, a modified dosage schedule
necessary. Consider each patient individually utilizing the following guideline: In adults, initial loading dose is 750 mg. and maintenance
is 500 mg. at following time intervals: creatinine clearance >20 ml./
6-12 hours between doses; creatinine clearance 15-19 ml./min., 12-2
hours between doses; creatinine clearance 10-14 ml./min., 24-40 hou
between doses; creatinine clearance 5-9 ml./min., 40-50 hours betwe
doses; creatinine clearance <5 ml./min., 50-70 hours between doses. Further modification may be necessary in children.

HOW SUPPLIED

ANSPOR (cephradine, SK&F) Capsules—250 and 500 mg.

'ANSPOR' for Oral Suspension—Pleasant fruit-flavored oral suspension which, after reconstitution, provides 125 mg. or 250 mg. of cephradine
5 ml. teaspoonful.

SK&F Smith Kline & French Laboratories
Division of SmithKline Corporation, Philadelphia, Pa. 19101

A New Oral Antibiotic

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PAIN RELIEF FOR THE MAJORITY

NO.4—for pain intensity below the need for injectables

As a rule, only pain that requires morphine is beyond the scope of Empirin® Compound with Codeine No. 4. That's because it delivers a full grain of codeine. (In the preferred phosphate form.) Its antitussive action is particularly appreciated by patients with fractured ribs, and following chest or abdominal surgery. Its low addiction liability is a bonus for all patients who require potent analgesia.

(III)

NO.3—for almost all other kinds of lesser pain

Most other kinds of lesser pain respond to Empirin Compound with Codeine No. 3—whether musculoskeletal, neurological, soft-tissue or visceral. One might say No. 3 is an "all-purpose" analgesic — not too little, not too much. Just right for your out-patients in these categories.

Wellcome

Burroughs Wellcome Co.
Research Triangle Park
North Carolina 27709

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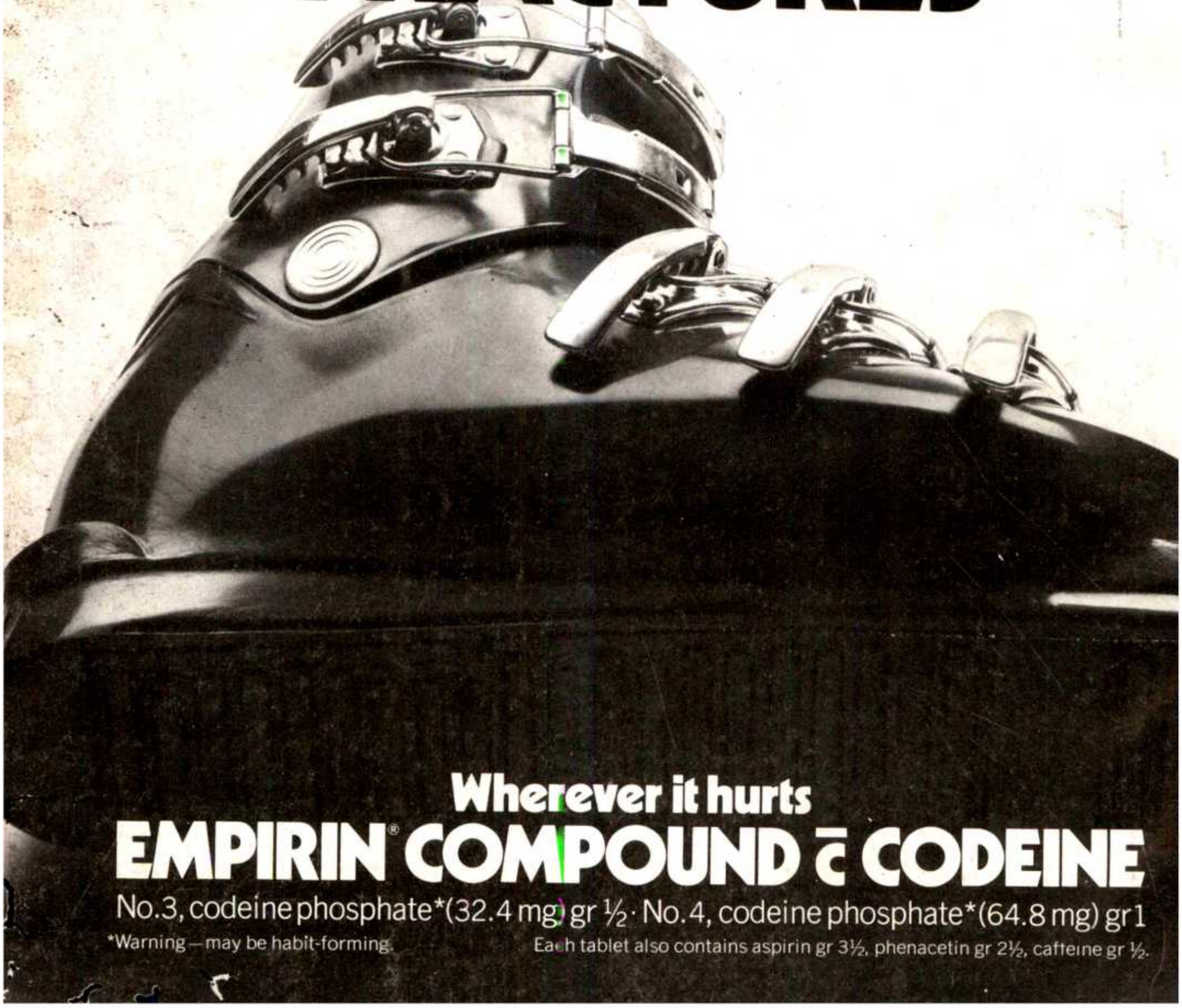

Wherever it hurts

EMPIRIN® COMPOUND c̄ CODEINE

No.3, codeine phosphate*(32.4 mg) gr ½ · No.4, codeine phosphate*(64.8 mg) gr 1

*Warning—may be habit-forming.

Each tablet also contains aspirin gr 3½, phenacetin gr 2½, caffeine gr ½.